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HEART FAILURE AFTER MYOCARDIAL INFARCTION;  
CONTEMPORARY TRENDS, DETERMINANTS AND  
PROGNOSTIC IMPLICATIONS –  
NATIONWIDE OBSERVATIONAL STUDIES

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# HEART FAILURE AFTER MYOCARDIAL INFARCTION; CONTEMPORARY TRENDS, DETERMINANTS AND PROGNOSTIC IMPLICATIONS - NATIONWIDE OBSERVATIONAL STUDIES

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*Du kan. Inget berg är brant.  
Om du tror blir det sant. Du kan!  
Lejonkungen*

***To my mother***



## ABSTRACT

Coronary artery disease (CAD) is one of the leading causes of heart failure (HF). The overall aim of this thesis is to describe contemporary epidemiology of post myocardial infarction HF including temporal trends, changes in patient characteristics, its determinants and prognostic implications, as well as the long-term risk of HF admission. We also examined adherence patterns to beta-blocker treatment after acute myocardial infarction (AMI) and subsequent implications on outcome using a nationwide myocardial infarction registry.

The thesis includes four papers. The first paper described the incidence, temporal trends, and prognostic impact of HF complicating acute AMI. The second paper investigated the incidence, determinants and prognostic implications of HF with normal ejection fraction (HFNEF) that occurs in the setting of AMI. The third paper investigated the risk and predictors of HF admission among survivors of AMI. Finally, the fourth paper investigated the pattern of adherence to beta-blocker treatment in one-year AMI survivors, and assessed predictors of better adherence and subsequent implications on long-term all-cause mortality and/or HF admissions.

The incidence of in-hospital HF during an index hospitalization for AMI decreased by 39% with an absolute risk reduction (ARR) of 18% over 13 years with more pronounced reduction among STEMI (ARR 22%) than NSTEMI (ARR 14%) patients,  $p < 0.001$ . The use of rapid revascularization treatment and evidence-based pharmacologic treatment increased over the years (1996-1997 vs. 2008). Patients with clinical HF after AMI had a higher risk for death (adjusted HR: 2.09; 95% CI: 2.06 to 2.13). However, mortality was decreasing over time, showing the potential for a further decrease with even better treatment strategies.

HF with normal EF was a relatively less common form of HF in the setting of AMI but its occurrence was associated with at least a 3-fold increase in mortality compared to patients with NEF and no HF. Interestingly, patients who had evidence of left ventricular systolic dysfunction (LVEF  $< 50\%$ ) without clinical HF had better long-term prognosis than patients with HFNEF, underscoring the importance of clinical findings such as pulmonary rales to predict higher risk of mortality complementary to EF.

Long-term survivors of MI without a previous history of HF remain at risk of late-onset HF (LOHF) with in-hospital HF being a strong predictor. Out of 150,566 AMI survivors without prior HF, 19.4% ( $n=29,194$ ) were readmitted due to HF during the study period (2004-2013). However, the incidence of LOHF after AMI showed a declining trend over the years which largely seems to be related to a decreasing burden of comorbidities and an improved evidence-based revascularization strategy and pharmacologic treatment.

Out of 38,597 one-year AMI survivors, 31.1% were non-adherent to beta-blocker treatment one year after the index event. Patients with LVSD (REF) without signs of HF and patients with HFREF were more likely to receive beta-blockers at discharge and adhere to treatment one year after the index AMI. Better adherence was associated with improved long-term outcomes in all patients except in patients with HFNEF. Of note, the long-term prognostic advantage seen also in low-risk patients highlights the need for future studies.

In conclusion, though gains have been made in AMI treatment, the lingering problem of HF underscores the importance of interventions at all levels that mitigate its occurrence starting from primordial preventive measures, early identification and treatment of risk factors, prompt and effective treatment of AMI and implementation of evidence-based secondary prevention therapies while ensuring the continuous monitoring of epidemiological trends.

# LIST OF SCIENTIFIC PAPERS

The present thesis is based on the following papers, referred to in the text by their Roman numerals:

- I. Liyew Desta, MD, Tomas Jernberg, MD, PhD, Ida Löfman, MD, Claes Hofman-Bang, MD, PhD, Inger Hagerman, MD, PhD, Jonas Spaak, MD, PhD, Hans Persson, MD, PhD

*Incidence, Temporal Trends, and Prognostic Impact of Heart Failure Complicating Acute Myocardial Infarction in the SWEDEHEART registry: A Study of 199,851 Patients Admitted With Index Acute Myocardial Infarctions, 1996 to 2008.*

JACC Heart Fail. 2015 Mar;3(3):234-42.

- II. Liyew Desta, MD, Tomas Jernberg, MD, PhD, Claes Hofman-Bang, MD, PhD, Jonas Spaak, MD, PhD, Hans Persson, MD, PhD

*Heart Failure with normal ejection fraction is uncommon in acute myocardial infarction settings but associated with poor outcomes: a study of 91,360 patients admitted with index myocardial infarction between 1998 to 2010.*

Eur J Heart Fail. 2016 Jan;18(1):46-53.

- III. Liyew Desta, MD, Tomas Jernberg, MD, PhD, Claes Hofman-Bang, MD, PhD, Jonas Spaak, MD, PhD, Hans Persson, MD, PhD

*Risk and Predictors of Readmission for Heart Failure following a Myocardial Infarction between 2004-2013: A Swedish Nationwide Observational Study.*

Submitted

- IV. Liyew Desta, MD, Masih Khedri, MD, Tomas Jernberg, MD, PhD, Pontus Andell, MD, PhD, Moman Aladdin Mohammad, MD, Claes Hofman-Bang, MD, PhD, David Erlinge, MD, PhD, Jonas Spaak, MD, PhD, Hans Persson, MD, PhD

*Adherence to Beta-blockers and Long-term risk of Heart failure and Mortality after a Myocardial Infarction: a study of 40,697 patients in the SWEDEHEART registry*

Submitted



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## LIST OF ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
ARB	Angiotensin II Receptor Blockers
ARR	Absolute risk reduction
AMI	Acute Myocardial Infarction
CABG	Coronary Artery Bypass Graft
CCU	Coronary-care unit
CAD	Coronary Artery Disease
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiography
EF	Ejection Fraction
HFNEF	HF with Normal EF
HFREF	HF with reduced EF
HFPEF	HF with preserved ejection fraction
HF	Heart Failure
HR	Hazard ratio
ICD-10	International Classification of Diseases
NSTEMI	Non-ST-elevation myocardial infarction
LOHF	Late-onset HF
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
PCI	Percutaneous Coronary Intervention
STEMI	ST-elevation- myocardial infarction
SWEDHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended therapies



# 1 INTRODUCTION

## 1.1 HISTORICAL PERSPECTIVES

### 1.1.1 Heart failure

Heart failure (HF) is a global problem of our time, that has been known since ancient times<sup>1</sup>. The earliest reported case of chronic HF dates back over 3500 years to the remains of an Egyptian dignitary who lived under the reign of the 18th dynasty Pharaoh Thutmose III (1479–24 BC). On a recent histopathologic examination of the lungs, pulmonary edema due to HF was proposed as the likely cause of death<sup>2</sup>. Hippocrates (467-377 B.C) described pulmonary rales and detailed symptoms of HF. He also discussed a rather modern way to drain fluid from the chest through a hole drilled in the ribcage. Galen (c.130 AD – c.210 AD), viewed the heart as the source of heat and thought that the heart's primary function was to distribute heat to the body. His opinions were to dominate Western thinking for more than 1500 years<sup>3,4</sup>.

Several centuries had elapsed before William Harvey clearly described circulation and provided the basis for understanding the hemodynamic abnormalities in HF in 1628<sup>5</sup>. A few centuries later a turning point occurred after the discoveries of Frank in 1895 and Starling in 1918 (Frank-Starling law) when a more biologically oriented research for regulatory mechanisms of heart function was initiated<sup>6</sup>.



*“... When edema is gross and fails to respond... Southey’s tubes constitute a cleaner way of removing fluid...”*

*Paul Wood. Heart failure. In Diseases of the heart and circulation. 1957;311*

Blood-letting and leeches were used for centuries as treatment of HF<sup>7</sup>. The benefits of digitalis were described by Withering in 1785<sup>7</sup>. In the 19<sup>th</sup> and early 20<sup>th</sup> centuries, HF associated with excessive fluid retention was treated with Southey's tubes.

The understanding of HF was significantly advanced in the 1940s and 1960s by the introduction of cardiac catheterization<sup>8</sup> which enabled characterization of many forms of structural heart disease. In the decades before the 1980s, the changes occurring in HF were related to the backward/forward theories and treatment was based on bed rest, inactivity and fluid restriction. Digitalis and diuretics constituted the mainstay of pharmacologic treatment by then<sup>3</sup>.

The description of Starling Curves<sup>9</sup> introduced the idea of myocardial contractility. Despite the difficulties in measuring contractility, the prevailing view was that contractility was reduced in patients with chronic HF and that increasing it would have a positive effect<sup>10</sup>. However, most clinical trials of inotropic drugs were stopped prematurely because the agents did more harm than good and none had a positive effect on survival<sup>11</sup>. Later, cardiac glycosides were also found not to improve survival in patients with HF in sinus rhythm<sup>12</sup>.

One important event took place in cardiology in December 1967, when Christian Barnard conducted the first orthotopic heart transplant in Cape Town, South Africa. The 1960s was also the decade that saw the emergence of LV assist devices (LVADs)<sup>13, 14</sup>. From the mid-1970s, the availability of vasodilators provided a means to reduce afterload<sup>15</sup>. However, it soon emerged that despite the benefits related to their hemodynamic effects, a series of trials showed that patients treated with these agents were at greater risk of developing worsening HF and mortality than those treated with placebo<sup>16-18</sup>.

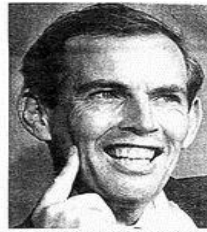
In the 1980s, the importance of non-hemodynamic abnormalities in HF were realized, when the neurohumoral response to reduced cardiac output was found to have a major adverse effect on long-term survival. The neurohumoral response was recognized as a compensatory response for short-term hemodynamic challenges like exercise and hemorrhage, which has harmful effects when the response is sustained<sup>19-23</sup>. In HF, blood pressure and cardiac output are reduced over long time periods. Therefore, the neuroendocrine response is chronically activated, with deleterious consequences as the persisting increase in catecholamines and the renin-angiotensin system (RAS) damages the function and structure of myocytes leading to fibrosis.

# Moments in History

In December, 1967, a young woman, Denise Darvall, was walking across a street in Woodstock to buy a cake when a car struck her. She died in Groote Schuur Hospital and in doing so achieved immortality by becoming the world's first heart donor when Christiaan Neethling Barnard transferred her heart into the chest of Louis Washkansky.

Cape Town has been witness to many historic moments since the day Van Riebeeck anchored in Table Bay. Few, if any, brought more limelight to the city than the heart transplant. For the surgeon, Dr Barnard, soon to be a household name throughout the world, "the heart is merely a pump". But for those who equated the heart with love and death, the transplant seemed close to a miracle.

"Mr Louis Washkansky, the 55-year-old Cape Town man whose life is being sustained today by the heart of a dead 23-year-old woman after the world's first successful heart transplant yesterday, is conscious in Groote Schuur Hospital and in a satisfactory condition." Monday, 4th December 1967



Professor Christiaan Barnard, leader of the heart-transplant team, in a characteristic pose during one of his many press conferences.



First close-up photograph to be taken of Mr Louis Washkansky, who underwent the world's first heart-transplant operation, was taken by a nurse using an Arca flash-camera's camera at Groote Schuur Hospital. Mr Washkansky, whose condition was given as good, is being assisted to breathe by a respirator. 4.12.1967

## *Dr Barnard and the first patient who received a heart transplant.*

One important piece of evidence proposing HF to be much more than a hemodynamic syndrome came from studies of beta-blockers which, in spite of causing initial worsening of hemodynamics, improved prognosis<sup>24,25</sup>. As a result of improved pathophysiologic understanding of HF, angiotensin converting enzyme inhibitors (ACEIs) and beta-blockers were successfully introduced as effective treatments for HF<sup>24-28</sup>. Later, mineralo corticoid receptor antagonists (MRA)<sup>29,30</sup> and the angiotensin receptor blockers (ARBs)<sup>31,32</sup> joined the group of drugs that counteract neuroendocrine activation.

The role of implantable cardioverter-defibrillators (ICDs) in preventing arrhythmia related mortality in HF patients was established in the beginning of the 21<sup>st</sup> century although the first device was implanted a few decades earlier<sup>33</sup>. A few years later cardiac resynchronization therapy (CRT) was shown to enhance ventricular contractility, diminish secondary mitral regurgitation, reverse ventricular remodeling and sustain the improvement in ejection fraction (EF)<sup>34,35</sup> and subsequently became established treatment of HF in appropriately selected patients. Other therapeutic technologies are continuously providing new advances in left ventricular assistance such as implant-based multi-parameter telemonitoring<sup>36</sup>, chronic vagal stimulation<sup>37</sup> and cardiac contractility modulation though the available evidence is considered insufficient to support guideline recommendations. The electronic revolution has enabled cardiologists to monitor heart function at a distance by wireless technologies.

Furthermore, new therapeutic possibilities for HF are being investigated in the fields of molecular biology, genetics and stem-cell therapy with substantial hopes<sup>37</sup>.

New pharmacological treatments were also introduced in the later years. The PARADIGM - HF study recently showed a dual angiotensin receptor and neprilysin inhibition (ARNi) with sacubitril/valsartan (LCZ696) significantly improved prognosis compared with Enalapril<sup>38</sup>. The same drug is being studied in patients with HF with preserved EF (HFPEF) while other ongoing trials are investigating various new classes of drugs developed from advances made in the pathophysiological understanding of HF.

Moreover, the advent of HF clinics has improved adherence and dosing of evidence-based treatment while contributing to improved self-care behavior through patient education and physical training programs, with subsequent improvement of survival and reduction in HF related events <sup>39</sup>.

Indeed, much has happened throughout the history of HF but there is much which remains to happen. While modern medicine has come a long way in the treatment of HFREF, HF with preserved EF (HFPEF) and acute HF remain two areas with large unmet needs for pathophysiological insights and improved therapies.

### **1.1.2 Coronary artery disease**

Angina pectoris, the main symptom of coronary artery disease (CAD) was first clinically described in the late 18<sup>th</sup> century <sup>40</sup>. The pathogenesis was unknown up until early 19<sup>th</sup> century. Almost a century had passed after the description of angina before pathologists recognized the importance of the coronary arteries in its pathogenesis. At the turn of the 20<sup>th</sup> century pathologists related acute myocardial infarction (AMI) with thrombosis in the coronary arteries. In the early 20<sup>th</sup> century, a number of cases of AMI were described and by 1919 electrocardiography was able to diagnose the disease<sup>41</sup>. By that time, the recommended treatment was total bed rest. In-hospital mortality was close to 40%, and many victims likely succumbed to early malignant arrhythmias and pulmonary embolism due to prolonged immobilization. The management of AMI constituted these approaches until the mid-20<sup>th</sup> century<sup>42</sup>.

Physiologists were able to characterize pressures in the major vessels and heart chambers of animals in the 19<sup>th</sup> century<sup>43</sup>. The cumulative effect of their efforts led to the first human heart catheterization, performed by Werner Forssman on himself in 1929, which led to a much better understanding of cardiac hemodynamics <sup>44</sup> and paved the way for the development of coronary arteriography in 1958<sup>45</sup>. These advances were of paramount importance in the development of the first revascularization strategy, coronary artery bypass grafting (CABG)<sup>46</sup>,

<sup>47</sup>.

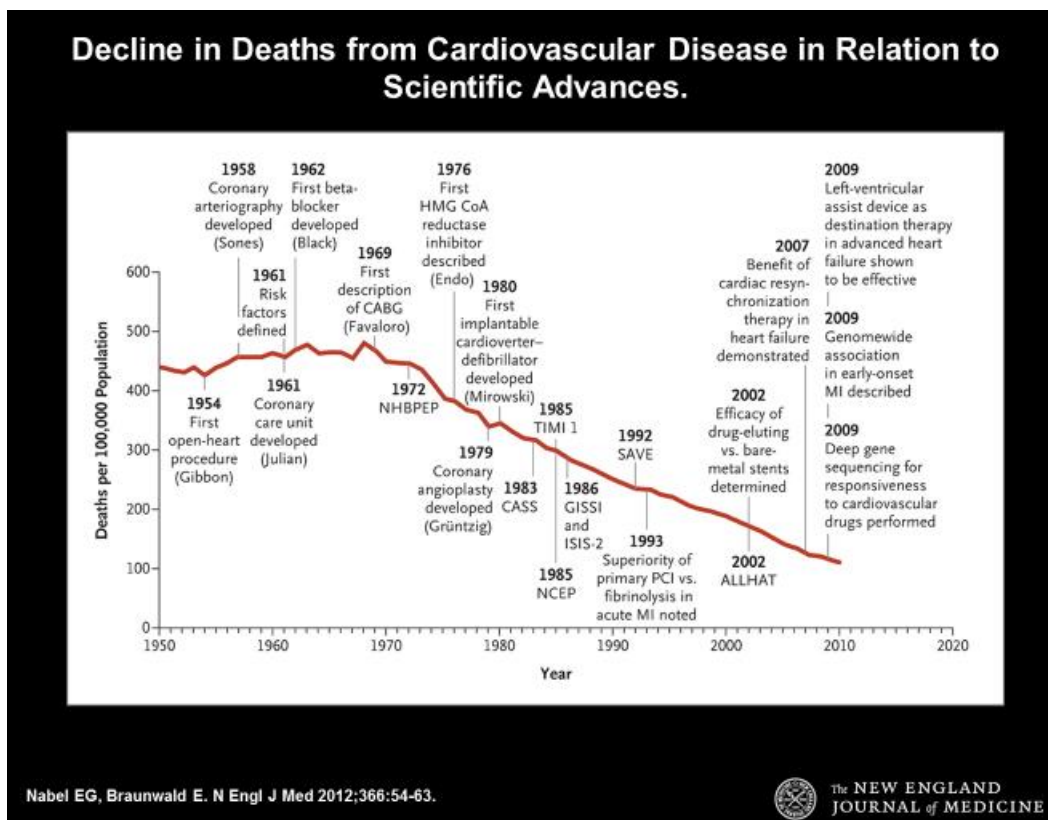


Other crucial developments were also taking place during the same time-period. The Framingham study was started in 1948 with the collaboration of professionals from different disciplines with the goal of understanding the mechanisms behind CAD by analyzing lifestyles in the population. Their findings identified high blood pressure and elevated lipid levels as definite risk factors. Later, smoking was identified as another major risk factor for the development of CAD. The recognition of these risk factors introduced the idea that CAD and its complications could be prevented. Educating clinicians and the public about these risk factors have led to huge improvements in age-adjusted cardiovascular death rates <sup>42</sup>.

The first major advance in the treatment of AMI came prior to the advent of CABG and percutaneous coronary interventions (PCI) in the early 1960s with the development of dedicated coronary intensive care unit after Day<sup>48</sup> and Brown et al <sup>49</sup> reported their initial experiences with the clustering of patients with AMI in special care areas designed for continuous monitoring of the electrocardiograms. The in-hospital mortality for MI patients was halved with the addition of coronary intensive care units (CCUs). A few years later Killip and Kimball performed a study of specialized care for myocardial infarction involving 250 patients with objectively proved AMI treated in a specially designed, equipped and staffed coronary care unit in a voluntary teaching hospital<sup>50</sup>. To provide a clinical estimate of the severity of myocardial derangement, they classified patients into one of four categories recognizing HF as a deleterious complication of AMI:

1) No heart failure (HF); 2) HF as demonstrated by the presence of basilar rales, an S3 gallop, and/or elevated jugular venous pressure; 3) Severe HF or frank pulmonary edema; and 4) Cardiogenic shock. This system later became known as the Killip classification, which we still use today. Its implementation in practice has since evolved to guide management and prognosticate while serving as an important tool for tracking outcomes in clinical research.

Another major advance took place in 1976 when the fibrinolytic agent, streptokinase was used to open acutely occluded coronary arteries by intracoronary infusion <sup>51</sup>. The GISSI trial showed that intravenous streptokinase reduced early mortality in patients with AMI <sup>52</sup>. Soon thereafter, the ISIS-2 trial showed that the addition of aspirin led to further reductions in mortality<sup>53</sup>. Subsequently, more potent platelet inhibitors (e.g., P2Y<sub>12</sub> and glycoprotein IIb/IIIa platelet–receptor blockers) were developed <sup>54</sup>. During that era, randomized, controlled clinical trials (RCTs) became established approaches for the advancement of effective treatments such as ACE-inhibitors<sup>55-58</sup>, angiotensin receptor blockers <sup>31</sup>, beta-blockers <sup>24, 25, 59-61</sup> and aldosterone blockers <sup>29, 30</sup>.



**Figure 1.** Decline in Deaths from Cardiovascular Disease in Relation to Scientific Advances. ALLHAT denotes Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, CASS Coronary Artery Surgery Study, GISSI Italian Group for the Study of Streptokinase in Myocardial Infarction, HMG-CoA 1-hydroxy-3-methylglutaryl coenzyme A, ISIS-2 Second International Study of Infarct Survival, MI myocardial infarction, NCEP National Cholesterol Education Program, NHBPEP National High Blood Pressure Education Program, PCI percutaneous coronary intervention, SAVE Survival and Ventricular Enlargement, and TIMI 1 Thrombolysis in Myocardial Infarction 1.<sup>42</sup> Used with permission from Nabel EG & Braunwald E., N Engl J Med 2012;366:54-63<sup>42</sup>

The 1960s and 70s heralded the emergence of the field of invasive cardiology. Andreas Grüntzig performed the first coronary balloon angioplasty in 1977, a few years after the pioneering work of Dotter and Judkins<sup>43</sup>. More than a decade later, RCTs demonstrated it to be more effective than thrombolysis and paved the way for the era of primary PCI<sup>54, 62</sup>. Balloon angioplasty was followed by the insertion of baremetal stents, and today, drug-eluting stents are used together with effective double antiplatelet treatment to prevent coronary restenosis<sup>63</sup>.

Indeed, notable advances have taken place over the last several decades which have improved the prognosis of patients with AMI impressively (**Figure 1**). However, HF remains a common complication after AMI occurring both as early and late complications and causing considerable morbidity and mortality.

## 1.2 DEFINITION OF HF

Heart failure is a common syndrome resulting from a variety of cardiac diseases and is characterized by a reduced cardiac output that is unable to meet the metabolic needs of the body. According to the 2016 ESC guidelines the diagnosis of HF requires<sup>33</sup>:

- the presence of appropriate symptoms, typically breathlessness or fatigue at rest or during exertion or ankle swelling and
- objective evidence of structural and/or functional cardiac dysfunction, resulting in a reduced cardiac output and/or elevated filling pressures at rest or during stress with accompanying signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema)
- In case of doubt, symptom improvement with HF therapy.

The first 2 criteria should be fulfilled in all cases. HF is a largely clinical diagnosis that is based on a careful history and physical examination.

### 1.2.1 Diagnostic criteria

Several standardized diagnostic criteria have been used for the purpose of case ascertainment on a large scale to study the epidemiology of HF. However, they lack uniformity<sup>64</sup> contributing to the discrepancies observed in the findings of studies on trends and outcomes. The ones used include the Framingham criteria<sup>65</sup>, the Boston criteria<sup>66</sup>, the Gothenburg criteria<sup>67</sup> and the European Society of Cardiology criteria<sup>68</sup>. The European Society of Cardiology criteria require objective evidence of cardiac dysfunction<sup>68-71</sup>. Altogether, the scores are largely similar for the detection of HF<sup>72</sup>.

### 1.2.2 Systolic and diastolic HF

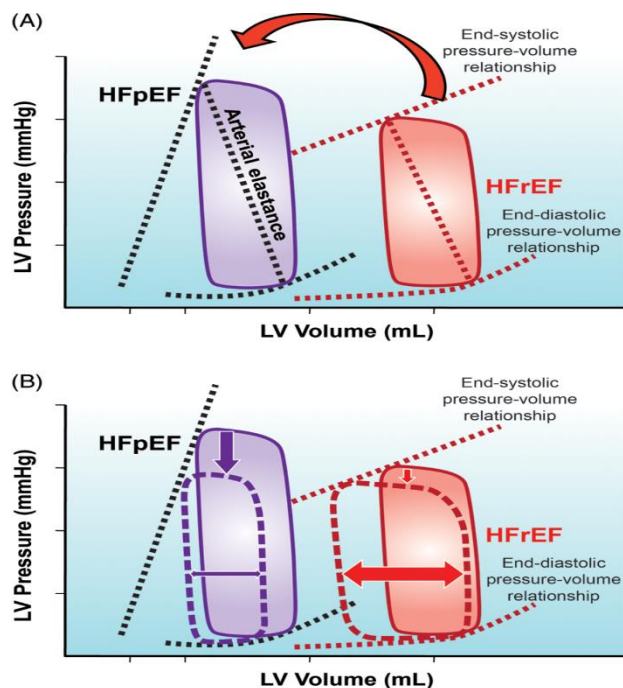
After establishing the diagnosis of HF, assessment of the LVEF is made to classify HF into HF with preserved (HFPEF) or reduced EF (HFREF). Systolic HF is identified by a reduced EF however different thresholds have been used by different groups<sup>73-77</sup>. A threshold of  $\geq 50\%$  remains the most commonly used<sup>77-83</sup>. Using this threshold, HFPEF constitutes more than half of HF cases in the population<sup>84, 85</sup>.

The 2016 ESC guidelines<sup>33</sup>, defines HFPEF by the presence of symptoms and/or signs of HF, a 'preserved' EF (defined as LVEF  $\geq 50\%$  or 40–49% for HF with medium range EF), elevated levels of natriuretic peptides and objective evidence of other cardiac functional (signs of elevated LV filling pressure) and structural alterations (left atrial enlargement and LV-hypertrophy). For confirmation of the diagnosis, a stress test or invasive assessment of LV filling pressures may be needed.

The two entities have distinct structural changes which are also associated with distinct functional consequences involving in particular the LV end systolic pressure–volume relationship (Figure 2) <sup>86</sup>.

The term ‘diastolic HF’ was first used to reflect the leading pathophysiological factor believed to cause the syndrome - LV diastolic dysfunction. However, patients with ‘systolic HF’ were even more likely to have moderate/severe diastolic dysfunction compared with patients with so-called ‘diastolic HF’. Nonetheless, progression of LV diastolic dysfunction was found to be a major mechanism distinguishing HFPEF.

There are still significant uncertainties surrounding the pathophysiology and treatment of HFPEF, leaving clinicians in a dilemma regarding its optimal management. New paradigms including a prominent role of co-morbidities, inflammation, endothelial dysfunction, and pro-hypertrophic signaling pathways have been proposed. The disease appears to be pathophysiologically distinct and not merely a continuum with HFREF <sup>86</sup>.



**Figure 2:** (A and B) Pressure–volume loop characteristics in HFPEF (black) and HFREF (red) in baseline conditions (A), and in response to vasodilators (B). Adapted and reused with permission from *Eur Heart J.*2014;35(16):1022-1032 <sup>86</sup>

In addition to etiological and phenotypic heterogeneity the prominent contribution of co-morbidities make understanding the HFPEF syndrome particularly challenging <sup>87</sup>.

### **1.3. EPIDEMIOLOGY**

#### **1.3.1 The scope of the problem**

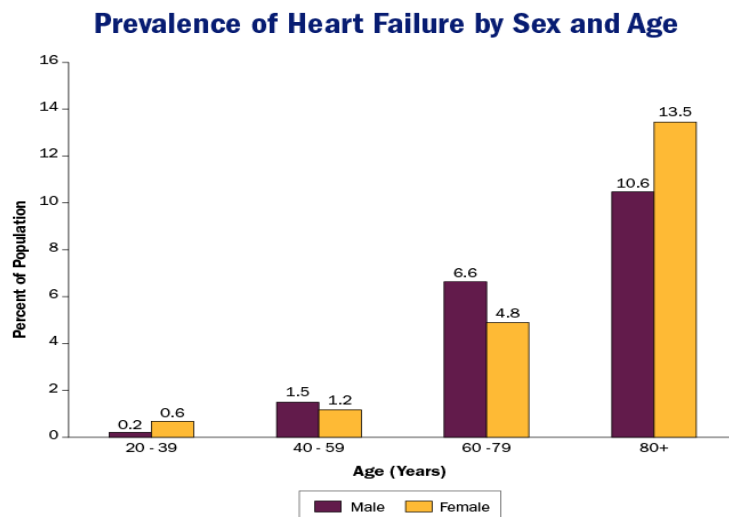
HF has become an important public health problem with increasing prevalence and economic burden on societies<sup>88, 89</sup>. In high income countries, HF is the most common diagnosis in hospitalized patients  $\geq 65$  years. HF carries a prognosis which is worse than that of most cancers<sup>37</sup>. Understanding the epidemiology of HF remains challenging, despite reports from large population-based studies, mostly from developed countries<sup>90-92</sup>. The reasons are related to difficulties in its diagnosis due to the non-specific nature of symptoms that may result from various cardiovascular and non-cardiovascular conditions that lead to impaired cardiac function.

Epidemiological studies have not employed a consistent definition of HF making comparisons difficult. The Framingham Heart study employed a clinical definition of HF without an objective assessment of ventricular function<sup>93</sup>. Other studies have included echocardiographic analysis of ventricular function in detailing the prevalence of HF<sup>94</sup>.

#### **1.3.2 Incidence and prevalence of HF**

The incidence of HF varies according to the populations studied and the definitions employed, and is dependent on age and sex. The incidence rate is estimated to be 1-4 per 1000 per year<sup>95, 96</sup>. Higher age and male gender are associated with higher incidences. Data from the Framingham cohort have shown a doubling in incidence of HF with each decade of ageing. Although incidence of HF is approximately one-third lower in general for women than men, women comprise about one-half of the HF burden due to their longevity<sup>97</sup>. Interestingly, women who suffer from a MI are more likely to develop HF than men<sup>97</sup>. Several common risk factors for HF, including hypertension, valvular heart disease, obesity, and diabetes mellitus, are more powerful predictors of HF risk in women than in men<sup>98</sup>.

The prevalence of HF is approximately 1-2% of the adult population in developed countries rising to  $\geq 10\%$  among people  $>70$  years of age. It increases with age, and is more common in men than in women in those aged  $>40$  and  $<80$  years (Figure 3).



**Figure 3:** Adapted and used with permission from Mozaffarian D, Benjamin EJ, Go AS, et al., on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association<sup>99</sup>

At the age of 40 years (or at 40 years old), the lifetime risk of development of HF is 1 in 9 for men and 1 in 6 for women. In those with a prior history of MI at age 40 years the lifetime risk for the development of HF is greater, being 1 in 5 for both men and women. As patients with CAD, hypertension and HF itself continue to live longer with better treatment, it is expected that the prevalence of HF will continue to rise. Furthermore, changing demography, increased prevalence of major CV risk factors such as hypertension, diabetes, and obesity as well as progressive chronic kidney disease (CKD) (add to abbreviations), may also contribute to an increase in prevalence over time. Worldwide, it is estimated that HF affects more than 38 million people<sup>37</sup> an increase from 23 million estimated in the 1990s<sup>100</sup>.

### 1.3.3 Morbidity and quality of life

Patients with HF are burdened not only by disabling symptoms, but also have high prevalence of comorbidities including hypertension, diabetes, atrial fibrillation and chronic pulmonary disease. They are also at higher risk of developing thromboembolic complications including stroke, MI and venous thromboembolism<sup>100-102</sup>. Clearly, therefore, patients with HF are likely to be dependent on frequent consultations with healthcare services, in both primary care and hospital settings. Such dependence exemplifies the demand HF places on health-care resources.

HF has a significant detrimental effect on quality of life which encompasses physical and psychological wellbeing, as well as social functioning.

Readmissions for HF remain common, with significant quality of life and economic repercussions. Multiple hospitalizations, particularly of elderly patients with multiple comorbid conditions, are especially common. In patients aged  $\geq 65$  years, the 30-day hospital readmission rate is approximately 30%<sup>103</sup>. Insights from large registries have revealed that approximately 20% of patients admitted with acute decompensated HF have no weight loss during their hospitalization,<sup>104</sup> suggesting the inadequacies of in-hospital management.

### **1.3.4 Prognosis**

Reports from the Framingham cohort have confirmed a decrease in long-term mortality with symptomatic HF. Nevertheless, the 10-year survival for patients with symptomatic HF remains only 20%, with a median survival of 1.7 years for men and 3.2 years for women<sup>90</sup>. Approximately 50% of patients diagnosed with HF die within 5 years<sup>91</sup>. The poor survival seen in the Framingham (US) data has also been observed in the European population with HF<sup>105</sup>. HF mortality increases with age and rises precipitously after 65 years of age. The 30-day inpatient hospital mortality is 11% in US patients aged  $\geq 65$  years admitted with HF<sup>103</sup>. Indeed, the 65-year age-adjusted and sex-adjusted mortality rate for HF is worse than for most common malignancies, including breast and prostate cancer<sup>106</sup>.

## **1.4 PATHOPHYSIOLOGY**

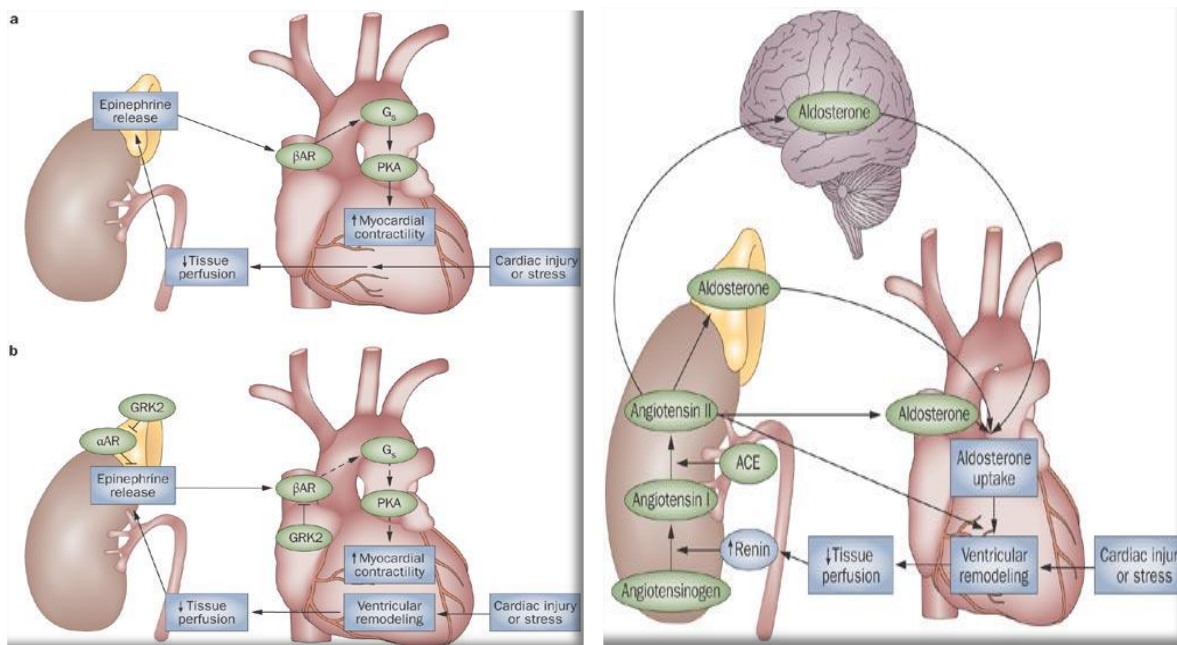
HF is the clinical syndrome that results from structural or functional abnormalities that impair ability of the heart to fill with or eject blood. A patient with HF has decreased cardiac output which in turn leads to decreased tissue perfusion. The body thus tries to maintain adequate tissue perfusion and compensates to bring mean arterial pressure back to normal using several mechanisms including the Frank–Starling mechanism, neurohormonal activation and ventricular remodeling. While initially beneficial, the long-term effects of these mechanisms serve to worsen HF in a vicious cycle if the adaptation persists<sup>107-109</sup>.

Cardiac insults that cause myocardial pressure overload, volume overload, or decreased contractility trigger adaptive responses whose purpose is to improve cardiac output and maintain blood flow to vital organs. However, when these responses become persistent, they lead to the structural and molecular changes that characterize ventricular remodeling.

Neurohormonal activation in response to decreased cardiac pump function consists primarily of increased sympathetic activation (SA) and upregulation of the renin-angiotensin-aldosterone system (RAS)<sup>110</sup> (Figure 4). Plasma norepinephrine (NE), an indirect measure of total SA is elevated and is associated with an increased risk of mortality. Increased SA is

associated with a number of deleterious effects on cardiovascular function, which can be reversed by pharmacologic blockade of sympathetic receptors <sup>111, 112</sup>.

### Activations of the Sympathetic and the Renin - Angiotensin - Aldosterone systems in heart failure



**Figure 4:** Used with permission from Dorn GW et al (2009), *Nat Rev Cardiol* <sup>113</sup>

Increased SA is accompanied by upregulated activity of the RAAS, causing salt and water retention and vasoconstriction<sup>114</sup>. Angiotensin II (AII) is a potent vasoconstrictor that acts on peripheral arterioles. AII production in HF increases afterload, wall stress, and myocardial oxygen consumption, ultimately decreasing stroke volume. AII stimulates both SA and aldosterone release. In addition, AII stimulation of the myocardium has been associated with activation of the fetal gene program, LV hypertrophy, and myocardial fibrosis. Aldosterone is a mineralocorticoid hormone that stimulates sodium reabsorption in the distal tubule. When combined with AII, the net effect is avid sodium reabsorption in both the proximal and distal tubules, contributing to volume overload in HF. Aldosterone also has been implicated in proliferation of myocardial fibrosis<sup>115</sup>. Treatment with neurohormonal blockers that interfere with SA and RAAS activity improves survival in patients with HF.

Natriuretic peptides, atrial natriuretic peptide (ANP), and B-type natriuretic peptide (BNP) are released from cardiomyocytes in response to increased atrial and ventricular wall stress. The pro-protein proBNP is cleaved into BNP and the physiologically inactive molecule NT-proBNP. Natriuretic peptides are degraded by neprilysin, a neutral endopeptidase. The natriuretic peptides have physiologic functions that counter the effect of sustained SA and



RAS activation, including decreasing RAS activity, inducing peripheral vasodilation and sodium excretion, and inhibiting myocardial hypertrophy and fibrosis<sup>116</sup>. Treatment with a combination angiotensin-receptor blocker/neprilysin inhibitor (ARNi) reduces the risk of death and hospitalization for HF<sup>38</sup>. Other neurohormonal mediators such as activation of arginine-vasopressin system, endothelin-1 and impaired Nitric oxide (NO) system function may have significant hemodynamic and ventricular remodeling effects<sup>117-119</sup>.

In summary, the chronic hemodynamic stresses on the heart lead to alterations in the size, shape, structure, and function of the ventricle in a process known as remodeling which is characterized by myocyte apoptosis, hypertrophy, tissue fibrosis, activation of metalloproteinases and increased cardiac expression of cytokines<sup>120-124</sup>. An intricate network of pathophysiological changes eventually leads to the clinical spectrum of features observed in patients with cardiac dysfunction.

## **1.5 ETIOLOGIES**

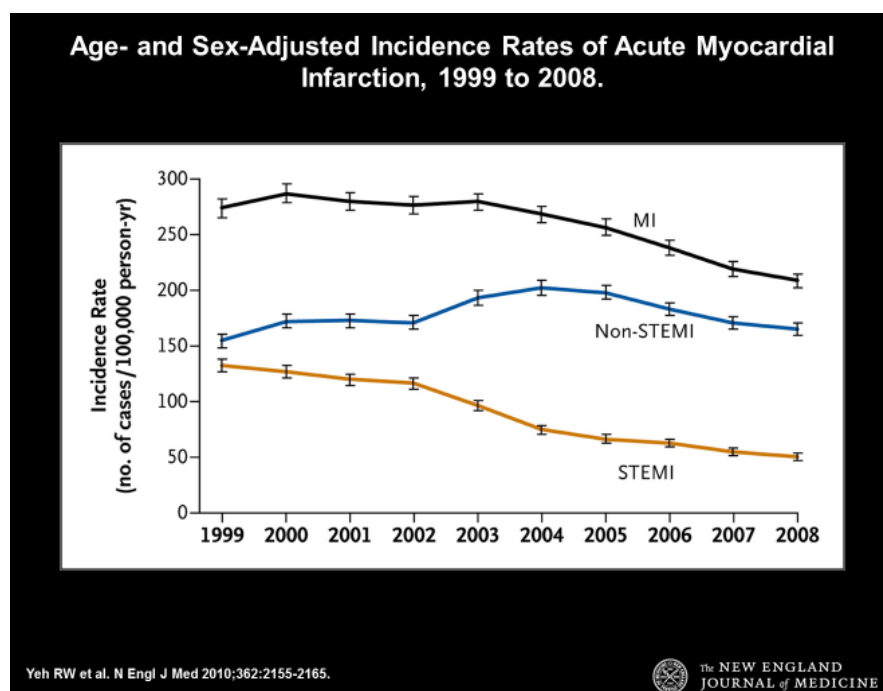
Longitudinal studies<sup>90, 125</sup> provide data relating to the etiologies of HF, and their respective contributions at different time periods. In the developed world, CAD and hypertension are the principal etiologies in the development of HF in almost 80% of patients with HF<sup>126</sup>.

However, the prevalence of CAD in studies of HF vary considerably. Clinical trials and population-based studies have reported estimates with large discrepancies<sup>95, 127-131</sup>. In the initial cohort of the Framingham study, hypertension appeared to be the most common underlying condition. However, as time progressed, an increase in the contribution of CAD (at the expense of hypertension and valvular heart disease) was noted. Consideration of the attributable risk of risk factors for HF and its evolution over time is important for prevention<sup>88</sup>. Other significant causes of HF include idiopathic dilated cardiomyopathy, hypertrophic and restrictive cardiomyopathies, and valvular heart disease.

## 1.6 HEART FAILURE AFTER MYOCARDIAL INFARCTION

### 1.6.1 Incidence and temporal trends of CAD and AMI

As outlined above, CAD is one of the leading causes of HF. AMI remains a major clinical problem despite reported declines in premature CAD in the developed world. Studies have shown decreases in the incidence and severity of acute myocardial infarction (AMI) which are partly ascribed to the growing use of coronary artery revascularization procedures and better medical treatment<sup>125, 132, 133</sup> though primarily attributable to a reduction in major risk factors<sup>134, 135</sup> with a marked decrease in the incidence of ST-segment elevation myocardial infarction (STEMI)<sup>135, 136</sup> (Figure 5). Effective primary and secondary prevention of coronary heart disease is therefore of paramount importance<sup>137</sup>. Data from the INTERHEART study show that most cases of MI are predictable from what is already known about the preventable risk factors<sup>138</sup>.



**Figure 5.** Adapted and used with permission from Yeh RW et al, *New Engl J Med* 2010;362(23):2155-65. I bars represent 95% confidence intervals. MI denotes myocardial infarction, and STEMI ST-segment elevation myocardial infarction<sup>135</sup>.

### 1.6.2 Incidence and prevalence of HF and LVSD after AMI

Over the years, population-based studies<sup>139, 140</sup>, registries<sup>141-147</sup> and clinical trials<sup>148-152</sup> have studied changes in the incidence, determinants and prognosis of HF and LVSD after AMI. While population-based studies usually report on longer-term follow-up and outcomes post-AMI, most data on the incidence of in-hospital HF and LVSD originate from clinical trials.

While some employed ICD-codes for case ascertainment, probably underestimating the incidence of HF, others utilized evaluation of case-records or patient reviews which is also biased by varying definitions of HF and differing study populations <sup>153</sup>.

Hence, the use of different approaches to quantify HF that complicates AMI makes comparison of the incidence and prevalence of HF after AMI difficult. However, collectively the studies suggest 30-50% of AMI patients have HF at some time following AMI <sup>139-152</sup>. Patients in clinical trials tend to generally be younger, more often men, often admitted at CCUs, with lower incidence of HF on arrival, and higher likelihood of receiving evidence based therapies including reperfusion treatments <sup>142, 149, 154</sup>. As a result, the reported incidence of HF after AMI is lower in trial patients than in epidemiologic studies. Of note, limited data are available regarding incidence and prognostic impact of HF with normal EF (HFNEF) in the setting of AMI that include detailed structural and functional assessment of diastolic function according to current guidelines<sup>33, 155</sup>.

Data on the incidence and prevalence of LVSD early after AMI is even more limited partly due to the inadequate attention given to it, despite the fact that it is one of the major precursors of HF. It is known that imaging evaluations are more likely to be performed in patients managed by cardiologists, in younger patients, in patients admitted to CCUs and in teaching hospitals, which increases the likelihood of a strong selection bias in the cohorts studied. In addition to methodologic issues in echocardiographic LVEF assessment, the utilization of other imaging methods and varying cut-offs for defining reduced LVEF influence classification of patients, making comparison of reported findings challenging <sup>70, 143, 144, 148, 150, 152, 155-160</sup> (Table 1). Clinical trials present more complete data on LVEF than do epidemiologic studies, however bias related to inclusion criteria in these studies is significant.

In one prospective population study, the prevalence of LVSD (defined as LVEF  $\leq 30\%$ ) was found to be approximately 30 per 1000 of the population aged 25 years and older, with approximately 50% of those with LVSD being asymptomatic<sup>161</sup>. The methodological issues discussed above account for the discrepancies reported in the incidence and prevalence of LVSD after AMI (Table 1).

### **1.6.3 Ventricular remodeling after AMI**

A large AMI can lead to changes in the structure of both the infarcted and non-infarcted regions of the myocardium. The process of progressive lengthening and secondary volume-overload hypertrophy occurs in the non-infarcted areas. This alteration affects both the function of the ventricle and survival. Acute reperfusion therapy has been shown to result in a

reduction in ventricular volume. Both experimental and clinical studies have shown favorable changes in the loading conditions of the left ventricle after a long-term therapy with an ACEI that prevents progressive ventricular enlargement<sup>162</sup>. Acutely, AMI can cause a severely dysfunctional ventricle due to massive myocardial ischemia and subsequent necrosis, usually presenting as cardiogenic shock. In some patients, acute HF may arise due to mechanical complications such as acute ventricular septal defect or papillary muscle dysfunction or rupture. Pump dysfunction in the peri-infarct period may alternatively be short-lived due to myocardial stunning or ischemia. The underlying cause for the majority of patients developing HF is a moderate amount of myocardial necrosis with consequent ventricular remodeling<sup>163, 164</sup>.

The process of ventricular remodeling starts in the immediate post-infarction period and continues slowly thereafter. It consists of ventricular wall thinning in the infarct area, ventricular chamber dilatation, and compensatory hypertrophy via lengthening of the non-infarcted portion of the myocardium<sup>162</sup>. The efficiency of the adaptive process depends on the prior health of the non-infarcted myocardium. Diabetic or hypertrophied myocardium may be less able to compensate for the area of infarction. Remodeling initially maintains stroke volume and pump function but over time these changes become maladaptive leading to decreased contractility and a vicious downward spiral culminating in HF<sup>163, 164</sup>. The process is causally related to neurohormonal activation as discussed in previous sections. The early studies on ACEI have shown attenuation of ventricular enlargement with prevention of further deterioration of ventricular performance<sup>55, 165</sup>.

#### **1.6.4 Clinical characteristics of patients with HF and LVSD after AMI**

The risk of HF during hospitalization for AMI is increased in elderly subjects, in women, and in patients with prior comorbidities such as diabetes, hypertension, pre-existing CAD, stroke and renal dysfunction<sup>141, 148, 149, 166</sup>. The Global Registry for Acute Coronary Events (GRACE) study showed that patients who develop HF in-hospital have a worse prognosis than patients who present with HF at admission<sup>166</sup>. Data from this and another study<sup>144</sup> showed no difference in the incidence of post MI HF between STEMI and non-STEMI patients while others reported a higher incidence of Killip class II-IV in patients with NSTEMI<sup>146</sup>. Those with marked LVSD were more likely to have had HF on admission and were more likely to develop fatal ventricular arrhythmias. HF is more common after anterior MI than after infarction at other sites<sup>102</sup>. Patients who develop smaller infarcts tend to be older with significant comorbidities and have a higher incidence of prior MI with subsequently higher likelihood of developing early-onset HF.

**Table 1: Studies on post Myocardial infarction HF/LVSD**

Study type	Period	N	Age mean	Prior MI	LVEF cut-off	Mode of LVEF-assessment	LVSD	HF %-adm/in-hosp	Scope of analysis	Trends incidence of HF
<b>Population</b>										
WHAS <sup>167</sup>	1975-1995	6,798		Recurrent	-	-	-		Early	Decreasing
WHAS <sup>139</sup>	1975-2001	10,440	72.5	Recurrent	-	-	-	39.9	Early	Increasing
Olmsted <sup>81</sup>	1979-1994	1,537		First	-	-	-	36	Early/ late	Decreasing
Olmsted <sup>140</sup>	1978-1998	2,171	73	First	-	Echo, MUGA	44%	24	All	No change in survival
Framingham <sup>92</sup>	1950-1989	546		-	-	-	-	-	Late	No change
Framingham <sup>168</sup>	1970-1999	676	67	First	-	-	-	24	Early/late	Increasing
Canada <sup>169</sup>	1994-2000	7,733	>65	First	-	-	-	37	Early/ late	Increasing
<b>Registries</b>										
French CCU <sup>143</sup>	1995	2,563	67	18%	≤50%	Echo	52%	44		-
French usic <sup>144</sup>	2000	2,320	65	18%	≤50%	Echo	46%	30.3		-
NMRI <sup>141</sup>	1994-2000	606,500	68.3		-	-		20.4 (+8.6)%		-
GRACE <sup>166</sup>	1999-2001	16,166	72.5	32%	-	-	-	13	Early	-
CCP <sup>142</sup>	1994-1995	42,703	77.3	32.8%	≤40%	Not given	26.6%	48.1		-
EHS ACS <sup>147</sup>	2000-2001	10,484	63.4	22.3%	-	-	-	35.2	-	-
Sweden <sup>170</sup>	1993-2004	175,216	35-84	-	-	-	-		All	Decreasing
Australia <sup>171</sup>	1984-1993	4,006	25-64	First	-	-	-	22.4	Early/Late	No change
<b>Clinical trials</b>										
BEAT <sup>148</sup>	1998-1999	3,166	68	28%	<40%	Echo	31.1%	55.5		-
InTIME II <sup>149</sup>	1997-1998	15,078	61	16%	-	-		23	-	-
VALIANT <sup>150</sup>	1999-2001	5,566	65.1	24%	≤40%	Not given	27.2%	23.1		-
GUSTO I/IIb/III, ASSENT <sup>151</sup>	1990-1998	61,041	61.7	-	-	-	-	29.4	-	-
TRACE <sup>172</sup>	1990-1992	6,676		35%	≤35%	Echo	39%			-
AIRE <sup>173</sup>	1991-1992	2006	65	-	-	-	-		Early	-
EMIAT <sup>157</sup>	1991-2001			28.5%	≤40%	MUGA	43%	53		-
ARGAMI-2 <sup>159</sup>	1996			12.6%	≤40%	Echo	28%	22		-
DIAMOND-MI <sup>158</sup>	1998			36.6	≤35%	Echo	29%	89		-
MAGIC <sup>152</sup>	1999-2002	6,213	70	26%	<50%	Not given		18.7		-
CAPRICORN <sup>174</sup>		1959	63	30%	≤40%	Echo		48		-

*AIRE, Acute Infraction Ramipril Efficacy; ARGAMI-2, Argatroban in AMI-2; ASSENT, Assessment of the safety and efficacy of a New thrombolytic; BEAT, Bucindolol Evaluation in AMI trial; CAPRICORN, Carvedilol Postinfarct survival Control in LV dysfunction; CCP, Cooperative Cardiovascular Project; CCU, Coronary Care Unit; DIAMOND-MI, Danish Investigations of Arrhythmias and Mortality on Dofetilide; EHS, European Heart Survey; EMIAT, European Myocardial Infarct Amiodarone Trial; Gusto I, Global Utilization of Streptokinase and tissue-plasminogen activator for Occluded Coronary arteries I; GUSTO IIb/III, Global use of Strategies to Open Occluded Coronary Arteries ; GRACE, Global Registry of Acute Coronary Events; InTIME, Intravenous NPA for the treatment of Infarcting Myocardium Early Study; MAGIC, Magnesium in Coronaries trial; MUGA, multiple Gated Nuclear Angiography; NRMI, National registry of MI; TRACE, Trandolapril Cardiac Evaluation; USIC, Unité de Soins Coronaires; VALIANT, Valsartan in AMI trial, WHAS, Worcester Heart Attack Study*

### **1.6.5 Prognostic value of HF following AMI**

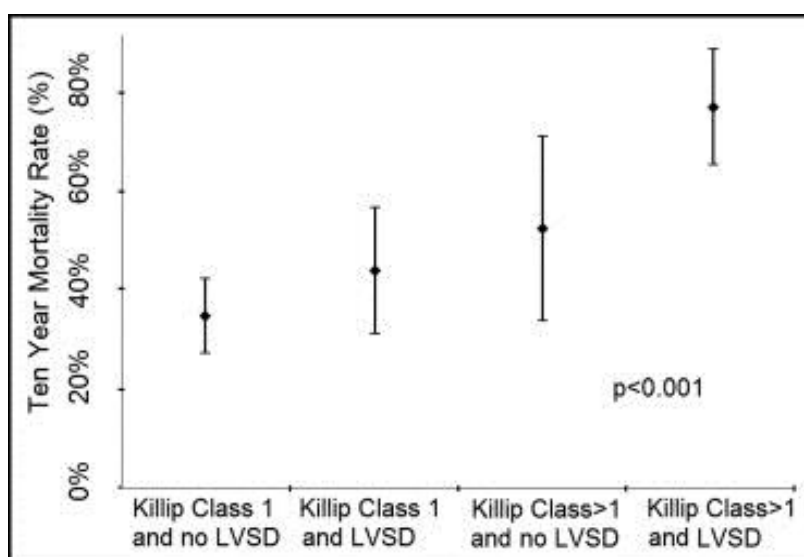
Several studies have demonstrated that HF after AMI increases in hospital mortality 2 to 4-fold<sup>141, 143, 144, 150, 166, 167</sup>. HF has also a detrimental effect on prognosis in the long-term. The timing of HF after AMI has been shown to effect prognosis. Development of HF during hospital stay is associated with a higher in-hospital mortality than presenting with HF during admission<sup>166</sup>. Post-MI HF also affects morbidity with significantly greater in-hospital incidences of re-infarction, stroke and sustained VT/VF compared to those without HF<sup>175</sup>. The appearance of pulmonary rales during hospitalization is one of the signs of an unfavorable hemodynamic state<sup>176</sup> and predict worse outcomes<sup>177</sup>. Higher Killip class is associated with poor long-term outcome<sup>177</sup>. In the AIRE trial which studied the efficacy of Ramipril in AMI patients with clinical HF evidence of HF was defined as at least one of the following: evidence of HF on chest radiograph; presence of bilateral rales or auscultatory evidence of a third heart sound with persistent tachycardia<sup>173</sup>.

### **1.6.6 Prognostic implication of LVSD after AMI**

Although relatively understudied compared to the prognostic implication of co-existing HF and LVSD after AMI, post myocardial infarction LVSD without clinical HF is associated with poor outcome. Studies have shown the detrimental effect of LVSD after AMI on both short and long-term prognosis, independently of HF<sup>150, 178-181</sup>.

### **1.6.7 Prognostic impact of both HF and LVSD after AMI**

The simultaneous presence of HF and LVSD is associated with even greater risk of morbidity and poor short- and long-term prognosis (Figure 10). Killip class and LVSD both predict mortality, and their combined presence predict a worse prognosis after myocardial infarction<sup>153, 182-184</sup> (Figure 6).



**Figure 6:** Impact of Killip class and left ventricular systolic dysfunction (LVSD) on 10-year mortality. Used with permission from Parakh K et al, *The American journal of medicine*. 2008;121(11):1015-8.<sup>182</sup>

### 1.6.8 HF/LVSD developing and recovering after discharge from the index AMI

A patient with post MI in-hospital HF will not necessarily develop chronic HF<sup>185</sup>. The TRACE study showed that in-hospital HF would be transient in approximately 15% of patients with major LVSD and 40% of patients without major LVSD<sup>186</sup>. Other prospective studies have shown improvement of the LVEF in up to 30-55% of AMI patients in a matter of weeks or months<sup>186-188</sup>.

The incidence of late-onset HF is even more uncertain. Data from the Framingham study suggested, late-onset HF (one month or more after discharge) may have been reduced by 50% while the Olmsted county study reported 41% would develop HF over 6,6 years. Three other studies (SAVE<sup>56</sup>, CAPRICORN<sup>174</sup> and EPHEUS<sup>30</sup>) reported subsequent HF event varying from 11.1% to 15.5% over 15 to 42 months follow up.

### 1.6.9 Temporal trends in incidence and prognosis of HF/LVSD after AMI

There is a paucity of contemporary data on changes in temporal trends in incidence and associated short and long-term outcomes of HF after AMI. Most of the studies performed over the last 3 decades suggest gradual reduction in the incidence of post MI HF over time<sup>141, 148, 149, 170, 179, 180, 189, 190</sup> while other studies reported an increasing trend<sup>139, 168, 169, 191, 192</sup>.

Differences in patient population, diagnostic approaches and applied definitions are likely reasons for differences in reported findings.

Studies have also reported conflicting outcomes on mortality trends. While some reported no significant reduction<sup>140, 190</sup> in one-year mortality in patients with HF after AMI over the years, others have reported a declining trend in mortality<sup>169, 193</sup>. Separation of mortality into in-

hospital and long-term subsets seems to suggest improved in-hospital outcomes over the last decades with unchanged 1-year mortality over time<sup>167, 169</sup>.

Indeed, myocardial infarction and HF are closely related health problems which impose a major burden on health care systems worldwide. Hence, it is essential to study how these two disease states, that are so closely related but also independent of each other, interplay in the modern era of coronary care units, PCI technology and effective medical therapy.

#### **1.6.10 Adherence to secondary prevention therapies**

Registries have been introduced with the aim of improving quality of care and adherence to guideline recommended therapies. Furthermore, the main focus has been improving prescription during discharge. However, the intended survival benefits of these medications cannot be achieved without sustained therapy.

Beta-blockers remain a cornerstone in the treatment of patients with CAD, especially post-MI. Most of the studies that established the positive effect of beta-blockers in ACS pre-date the modern reperfusion era but beta-blockers are still widely used<sup>194, 195</sup>. The place of long-term treatment especially in low-risk patients is uncertain<sup>196</sup>. There is a lack of randomized clinical trials in the modern reperfusion era investigating the role of beta-blockers in post MI patients without LVSD or HF, but a large observational study did not find a lower risk of cardiovascular events after ACS in these patients<sup>197</sup>.

Thus, studying adherence patterns to beta-blockers and subsequent effect on outcome after AMI in real-world patients would give valuable complimentary information in addition to giving insights regarding adherence to guideline recommended therapies.

#### **1.7 Pros and cons of observational studies and randomized clinical trials**

The highest level of scientific clinical evidence stems from prospective, randomized control trials (RCTs). Many trials are limited by the specific recruitment of patients using narrow inclusion criteria and multiple exclusion criteria, thereby limiting the trial's generalizability to real-world patients seen in practice settings. In addition, large scale RCTs are complex, expensive to perform and economic revenue is typically the primary incentive to initiate such trials. Consequently, many trials are too small to provide reliable estimates of the risk-benefit balance. In general, patients included in RCTs are younger, with fewer comorbidities and a lower risk of mortality<sup>198</sup>.



## **Registry based epidemiologic studies**

High-quality observational studies, based on large-scale registries and adequate statistical modelling, provide valuable evidence for the external validity of RCTs making them an important complement to RCTs. Furthermore, large-scale observational registries are well suited for descriptive studies to investigate associations between patient characteristics and risk of disease and mortality.

Today, studies based on databases, medical records and registries have become extensive in epidemiological research. Even though data collection in register-based studies differs from researcher collected data, all persons in a population are available and traditional statistical analysis focusing on sampling error as the main source of uncertainty may not be relevant<sup>199</sup>. The main strengths of registry based studies are that data already exists and valuable time has passed, study populations are more complete minimizing selection bias and data is independently collected. They also have the advantage of studying important clinical outcome measures rather than surrogate end-points. Large study populations provide the opportunity to study rare conditions and end-points. Their main limitations include the possibility that necessary information may be unavailable, data collection is not done by the researcher, confounder information is lacking, missing information on data quality and truncation at the start of follow-up making it difficult to differentiate between prevalent and incident cases and the risk of data dredging<sup>199</sup>.

Limitations that are inherent to all observational studies must be considered. Because patients are not randomized, it is significantly more problematic to prove causation between exposure (e.g. risk factor, treatment) and clinical outcomes of interest. One important weakness of registry studies of treatment effect is that differences between the groups usually generate bigger differences in measured “effect” than the real difference between the treatments. When a specific treatment is not randomly assigned, other factors such as the preference of the physician, the hospital and/or patient may influence the choice, or a concomitant disease unknown both to the patient and physician that causes a phenotype for which we are not able to adjust.

The problem with confounders in observational studies is commonly dealt with by using multivariate adjusted regression analysis, e.g., logistic regression or cox proportional-hazards regression. However, these methods also have their limitations and confounders, especially unmeasured confounders, can still result in biased risk estimates – even after adjustments using advanced statistical methods.

## **2 AIMS**

### **OVERALL AIM**

To describe contemporary epidemiology of HF that complicates AMI including changes in temporal trends, patient characteristics, determinants and prognostic implications as well as the long-term risk of HF readmission and evaluate compliance patterns to mainstay evidence-based secondary preventive therapies and implications on outcome using a nationwide myocardial infarction registry.

### **PAPER I**

To study temporal trends in the incidence of HF complicating AMI and its effect on prognosis in a large national cohort.

### **PAPER II**

To study incidence and predictors of HF with normal EF (>49%) during hospitalization for an index AMI and its implications on short and long-term patient outcomes.

### **PAPER III**

To study the risk, determinants and temporal trends of late-onset HF (LOHF) and the composite event of LOHF and/or death in hospital survivors of AMI in a large national cohort.

### **PAPER IV**

To study pattern and determinants of adherence to beta-blocker treatment after a first AMI and subsequent implications of adherence on risk of all-cause mortality and the composite of HF admission and/or death based on status of clinical HF and LV systolic function during hospitalization.

## **3 MATERIAL AND METHODS**

### **3.1 PATIENT POPULATION AND REGISTRIES**

This work is based on data collected in the SWEDEHEART register between 1996 and 2013 with additional data from the National population register, the National Patient Register (NPR), the National cause of death Register and the National register for prescribed drugs (NRPD).

#### **3.1.1 SWEDEHEART**

The Register of Information and Knowledge about Swedish Heart Intensive-Care Admissions (RIKS-HIA) database was established as a national quality registry in 1991 and further improved in 1995 and includes today all Swedish hospitals ( $n = 72$ ) that provide acute coronary care. The registry enrolls consecutive patients admitted to a coronary care unit or other specialized facility because of symptoms suggestive of an acute coronary syndrome (ACS). Information is collected prospectively for more than 100 variables including baseline characteristics, electrocardiography (ECG) findings, examinations, interventions, in-hospital complications, discharge medication and diagnoses<sup>200, 201</sup>. The variables in RIKS-HIA comply with the international Cardiology Audit and Registration Data Standards (CARDS)<sup>202</sup>.

The SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies) registry is the largest quality-of-care registry in Sweden and was started in 2009 by merging RIKS-HIA with 3 other nationwide cardiac registries. The Swedish Coronary Angiography & Angioplasty Registry (SCAAR) includes patients that undergo a procedure in any of the 29 cardiac catheterization labs in Sweden. The Swedish National Registry of Secondary Prevention (SEPHIA) includes patients under the age of 75 from the specialized cardiac outpatient care post-MI. Lastly, the Swedish Heart Surgery Registry includes patients undergoing any heart surgery procedure in one of the 8 thoracic surgery centres in Sweden. Recently, the trans-aortic valve replacement registry and the registry for cardiogenetics have also been added to SWEDEHEART.

The registry enrolls approximately 80,000 cases each year: 30,000 with ACS, 40,000 undergoing coronary angiography or angioplasty, 7,000 undergoing heart surgery, and 6,000 who are followed for 12–14 months for secondary prevention after acute coronary

syndromes (ACS). The registry is independent of commercial funding and is sponsored by Swedish health authorities only.

The primary aim of the SWEDEHEART registry is to enhance the continuous development of evidence-based cardiac care in Sweden, and to measure quality-of-care outcome parameters across the country in order to improve the cardiac health of the Swedish citizens. It has also increasingly become an important platform for conducting valuable research on CAD <sup>200</sup>.

According to the National Board of Health and welfare's report from December 2015, the registry captures close to 100% of patients undergoing angiography, angioplasty, or heart surgery and 84% of all AMI patients. While there are some regional differences, most regions have a regional coverage of 80-90%.

### **3.1.2 Validity of the register:**

To ensure the validity of the data entered in the registry, monitoring visits are performed once per year by specially trained monitors who visit different hospitals and compare information in hospital charts and the data entries demonstrating a 95% overall agreement.

### **3.1.3 Merging with other national registries**

Additional data is gathered by merging data from other important quality of care national registries. Mortality data were obtained by merging SWEDEHEART with the Swedish population register to ascertain vital status and date of death or last date of follow-up. The National Patient Registry (NPR)<sup>203</sup> was used to obtain data on comorbidities. The registry is nationwide and connected to all hospitals in Sweden and collects ICD (International Classification of Disease) diagnosis codes linked to all inpatient hospitalizations and specialized outpatient visits from 1987 and subsequently. Reporting to the NPR is mandatory and departmental reimbursements from the Swedish tax-financed healthcare system are wholly based on flat rates from the ICD diagnosis codes. In addition to comorbidities, the NPR was also used for cardiovascular endpoints. The National registry for prescribed drugs (NRPD)<sup>204</sup> was also used to gather data on previously dispensed prescriptions of secondary prevention medications for Paper IV.

Data from the components of SWEDEHEART and other national registries were merged into a single database with the use of the personal identification number unique to each Swedish citizen.

## **3.2 DEFINITIONS**

### **3.2.1 Acute myocardial infarction (AMI)**

In the beginning of the study period (1996-2001), AMI was diagnosed according to World Health Organization criteria from 1994<sup>205, 206</sup> combining symptoms, ECG changes, or both with an increase in a biochemical marker (mainly creatine kinase [CK]-MB) exceeding double the upper reference level. From late 2001, the European Society of Cardiology/American College of Cardiology/American Heart Association consensus document criteria for the diagnosis of AMI were adopted, using mainly troponin T or I levels exceeding the 99th percentile in a healthy population together with either typical symptoms or ECG-changes.

### **3.2.2 In-hospital HF**

In papers I-IV, a clinical definition of HF was used to define in-hospital HF. In-hospital HF was defined as the presence of pulmonary rales or administration of intravenous (iv) diuretics or usage of iv inotropic drugs, as documented in the RIKS-HIA protocol. Cardiogenic shock was defined as systolic blood pressure of  $\leq 90$  mmHg for  $>30$  minutes while hypovolemia is ruled out in the presence of signs of organ hypoperfusion or if cardiac index was  $<1.8$  l/min/m<sup>2</sup> or if iv inotropes or intra-aortic balloon pump (IABP) were used.

### **3.2.3 In-hospital HF and left ventricular systolic dysfunction (LVSD)**

In paper II, we combined in-hospital HF as defined above and LVEF to categorize patients based on presence or absence of HF and LVSD assessed by echocardiography and/or, in a small minority of patients left ventriculography. Patients were categorized in four groups. Those without HF and normal EF  $\geq 50\%$  (NEF), those with signs of HF and normal HF (HFNEF), those without HF and reduced EF  $<50\%$  (REF) and those with HF and reduced EF (HFREF).

### **3.2.4 HF admissions**

Paper III and IV assessed the risk of late-onset HF (LOHF) after discharge from the index AMI. Late-onset HF was diagnosed if a patient was diagnosed as having HF when the record for a new hospital admission obtained from the NPR included ICD 10 codes for HF (I50.0-

I50.9) as principal or secondary diagnosis. The composite event of LOHF or death was defined as readmission because of HF as principal or secondary diagnosis or death after discharge from the index AMI. A hospital diagnosis of HF in Sweden has been validated against ESC criteria for the definition of HF, with a validity of 95% for a principal diagnosis and 82% irrespective of position<sup>207</sup>.

### **3.2.5 Assessment of prescription and adherence**

Paper IV aimed at examining the pattern and associations with long-term outcome of adherence to long-term beta-blocker treatment in one-year survivors of AMI.

Prescription of beta-blocker drugs was determined from the RIKS-HIA protocol if the patient was prescribed any beta-blocker drug or not at time of discharge from the index event.

Adherence was determined as Proportions of Covered days (PDC). PDC was defined as the ratio between the numbers of days covered by the prescription claims of a certain drug, divided by the total number of days in the period. As in most previous studies, a threshold level for  $PDC \geq 80\%$  was used to classify patients as adherent or non-adherent<sup>208, 209</sup>.

## **3.3 PATIENTS AND METHODS**

### **3.3.1 PAPERS I & II**

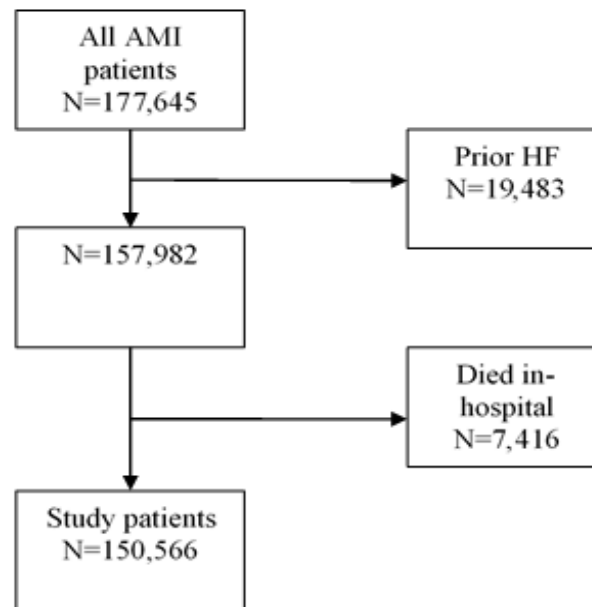
Paper I included an unselected cohort of 199,851 patients enrolled in the registry for the first time between 1996-2008 who fulfilled the criteria for the definition of AMI.

Paper II included 90,320 consecutive AMI patients enrolled in the registry between 1998 and 2010 with known left ventricular ejection fraction (LVEF) assessed by echocardiography (99.4%) or LV angiography (0.4%). Patients with unknown LVEF were excluded from the analysis. Descriptive analysis of baseline characteristics of patients with unknown LVEF was performed to account for differences in patient characteristics between those with known and unknown LVEF.

### **3.3.2 PAPER III**

In paper III, a total of 177,645 AMI patients who were entered in the SWEDEHEART registry for the first time between 2004-2013 were eligible. Among these, 19,483 were excluded from the study because of prior history of HF. An additional 7,416 patients were excluded due to in-hospital mortality as the main goal of the study was to study LOHF after

an index AMI assessed by hospitalization for HF (Figure 7). The final study population comprised a total of 150,566 AMI patients. Data on hospitalization for HF after discharge from the index AMI admission (up to 31-Dec-2013) were obtained from the national patient register and defined as a new hospitalization for HF as outlined above.



**Figure 7:** Study flow-chart - Patients who were included for the first time in the SWEDEHEART registry without prior history of HF and who were discharged alive after the index AMI. Shown are the remaining patients after each step of the inclusion criteria.

### 3.3.3 PAPER IV

In paper IV, patients admitted to Swedish coronary care units for a first AMI between 2005-2010 were identified in the SWEDEHEART registry (N=81,023). Patients who died in-hospital, with previous HF and those with unknown LVEF were excluded. A total of 40,697 patients comprised the study population for the final analysis. Adherence to prescribed beta-blockers was determined for one year by merging data from the National register for prescribed drugs and its implications on all-cause mortality and the composite endpoint of LOHF/death was studied.

**Table 2. Summary of the study population, sample sizes and study purposes.**

<b>Studies</b>	<b>Study population</b>	<b>Sample size</b>	<b>Study purpose</b>
<b>Paper I</b>	MI patients enrolled 1996-2008, SWEDHEART	199,851	Describe incidence temporal trends, determinants of post MI HF and effect on prognosis
<b>Paper II</b>	MI patients with known LVEF enrolled 1998-2010, SWEDHEART	90,320	Describe incidence of HF/LV-dysfunction, determinants of HFNEF and differences in prognosis
<b>Paper III</b>	MI survivors without prior HF enrolled 2004-2013, SWEDHEART	150,566	Study the risk of HF readmission after discharge from index AMI and its determinants
<b>Paper IV</b>	First time MI with no prior HF surviving hospital course enrolled 2005-2010, SWEDHEART	40,697	Study the pattern of adherence to betablockers after discharge, determinants and associations with HF readmission and/or mortality

### **3.4 END POINTS**

The incidence of in-hospital post AMI HF was studied in paper I. Paper II included data on LVEF in addition to HF. The variables that defined in-hospital HF were obtained directly from the RIKS-HIA protocol and were available for nearly all patients. Outcome measures used included in-hospital, thirty day, one year and long-term all-cause mortalities. In paper III, the endpoints studied were late-onset HF and the composite of late-onset HF and/or all-cause mortality. In paper IV the primary end-points were all-cause mortality and the composite of late-onset HF and/or all-cause mortality which were obtained from the NPR and the NDR and were available for all patients.



### **3.5 VARIABLES IN REGRESSION MODELS**

In all studies adjustment was made for several confounders in the logistic regression and cox proportional hazard models. For the estimates in the multivariable models to be stable, based on empirical data, there should be at least 10 events for each covariate included in the model. As there were a large number of outcomes in all studies, this recommendation was never a limitation in the number of variables included.

Adjustments were made for variables that were well-known risk factors, important in-hospital clinical characteristics and complications or therapies that could alter the outcome. The final model included those covariates that remained significant in predicting the outcome variable (using a p-value <0.05 for assessment of significance). Odds ratios and Hazard ratios were calculated with 95% confidence intervals for variables in the models.

### **3.6 MISSING VARIABLES**

In SWEDEHEART, variables can have missing data for different reasons, e.g., some variables are compulsory to register and some are not. For variables that are not compulsory, e.g., smoking status, value of creatinine, weight and height, there is missing data because the value has not been registered. For variables that are compulsory, there is often a category 'unknown' – a form of ad hoc imputation that should be treated as missing data (see below). Variables in SWEDEHEART have been introduced at different times, therefore data for variables which were not a part of the registry at a certain time are missing. Hence, the number of missing covariates in the analyses varied.

In paper I, which mainly is a descriptive study, we presented the number of patients for each covariate in Table 1. In papers II-IV analysis was performed in complete cases. To address differences in patient characteristics between the study population and patients that were excluded from the analysis, a separate analysis that summarizes the characteristics of patients who were not part of the analysis is presented in Paper II.

### **3.7 ETHICS**

Anonymity was protected by replacing the personal identification number with a serial number. In Sweden, quality-of-care registries are parts of the continuing development of improved routine healthcare, written consent for patient inclusion in the registries is therefore not needed. Patients are informed of quality-of-care registries and have the right not to participate, although very few exercise this right. The merging with other registries was

approved by the National Board of Health and Welfare. The regional Ethics Committee of Uppsala University and the regional Ethics Committee in Stockholm approved the studies.

### 3.8 STATISTICS

In baseline characteristics tables, data are presented as numbers and percentages for categorical variables. Continuous parametric variables are expressed as means ( $\pm$  standard deviation) and medians (IQR). Qualitative data were compared using Pearson's Chi-square test while quantitative data were compared using independent student t-test. In papers I and II, the incidence of clinical HF and LVEF/HF categories and estimated proportions of patients and their baseline characteristics, as well as mortality over time were evaluated by comparing cohorts of patients admitted over 2-calendar year periods. In papers I-III, trend tests were performed for the variables where we reported temporal trends using  $X^2$  test for trend employing the linear-by-linear model.

In all papers adjustment was made for several confounders in the logistic regression and cox proportional hazard models. Unadjusted odds ratios (ORs) with 95% CI were computed using univariable logistic regression and adjusted ORs with 95% CI were computed using multivariable logistic regression. Unadjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using univariable Cox proportional hazard models and adjusted HRs with 95% CI were computed using multivariable Cox proportional hazard models. Adjustments were made for variables that were well-known risk factors, and in-hospital clinical characteristics and complications or therapies that could alter the outcome. The final model included those covariates that remained significant in predicting the outcome variable (using a p-value  $<0.05$ ). In paper IV, crude and multivariable adjusted OR with 95% confidence intervals were reported. Multivariable adjustment was made using three models. In Model 1, OR was adjusted for factors that *should* affect prescription/compliance to beta-blockers (potential contraindications). In Model 2, in addition we adjusted for factors that, besides HF types, *could* affect prescription/adherence. In Model 3, we also adjusted for gender and socioeconomic factors (country of birth, civil status, educational level and income) in addition to factors in Model 1 & 2.

Endpoint rates were calculated with the Kaplan-Meier estimator and significance testing between groups were assessed with the log-rank test. Long-term mortality was presented as a Kaplan-Meier plots.

In paper III, models predictive of the composite of HF readmission/death and death are

calculated and presented together with Kaplan-Meier curve for HF readmission as outcome variables to handle the competing risk of death.

In paper IV, interaction tests were performed to calculate p-values for interactions and assess differences between subgroups in the association between adherence to beta-blocker treatment and long-term outcome.

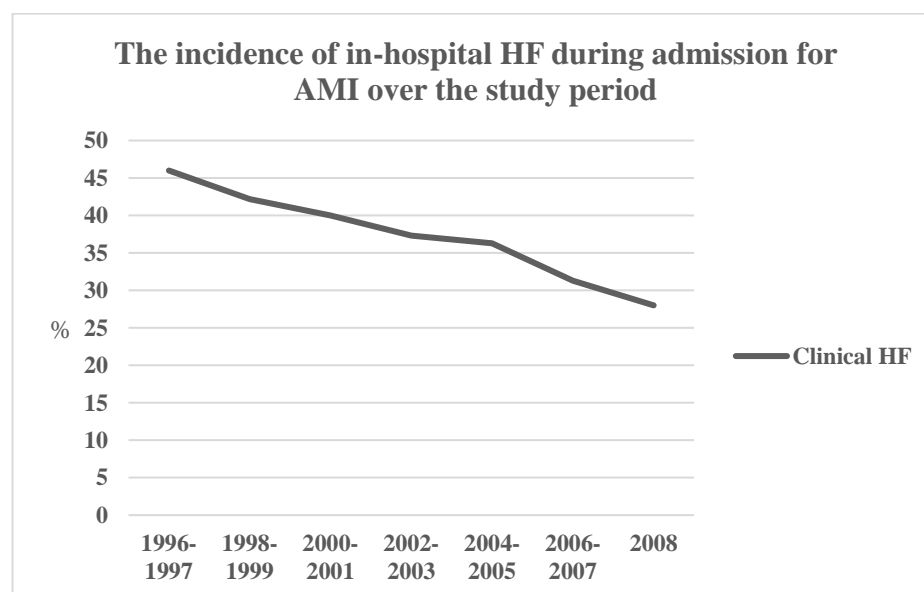
Outcome analyses were restricted to complete cases only; no imputations were performed. All analyses were performed using SPSS versions 19, 22 and 23 (IBM, Armonk, NY).

## 4 RESULTS

### 4.1 PAPER I

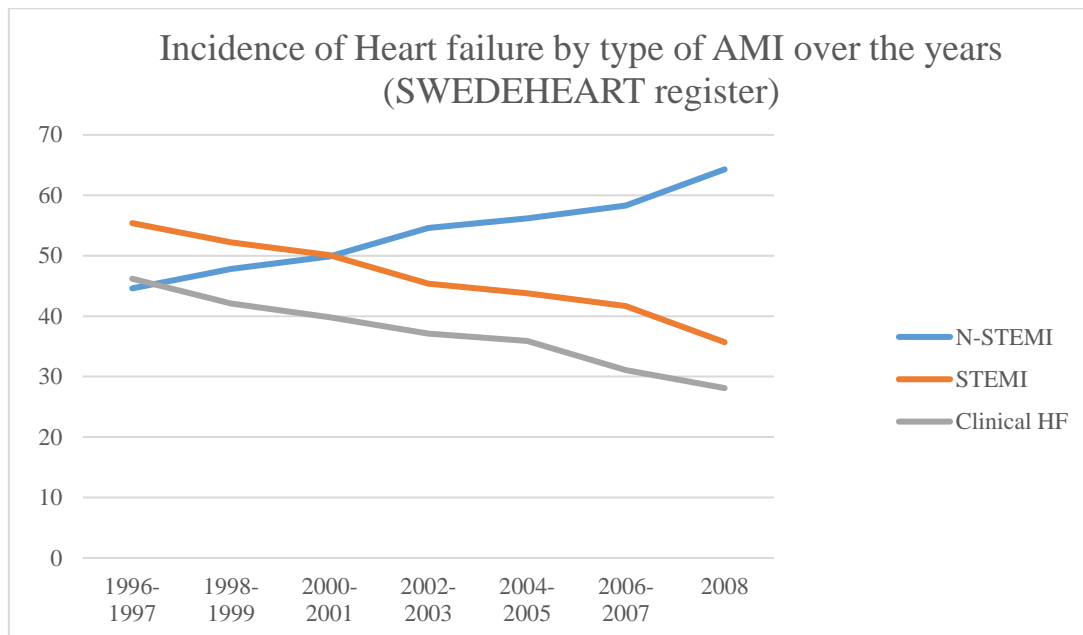
The mean age of the patients increased slightly (70 to 70.9 years) over the study period. The proportion of women increased modestly (35 to 37.1%). The burden of comorbidities such as diabetes mellitus (21.1% vs. 22.3%) hypertension (32.5% vs. 47%) increased across the study period (1996-1997 vs 2008) while the proportion of patients with history of prior AMI and previously known HF decreased from 17.8% to 10.6% and 11.7% to 9.7% respectively. (Table 1, Paper I)

The incidence of in-hospital HF declined from 46% during 1996-1997 to 28% in 2008 (RRR of 39% and ARR 18% ( $p < 0.001$ ,  $X^2$  test for trend) (Figure 8). Among patients with in-hospital HF, the proportion of women increased from 39% to 46% over the years.



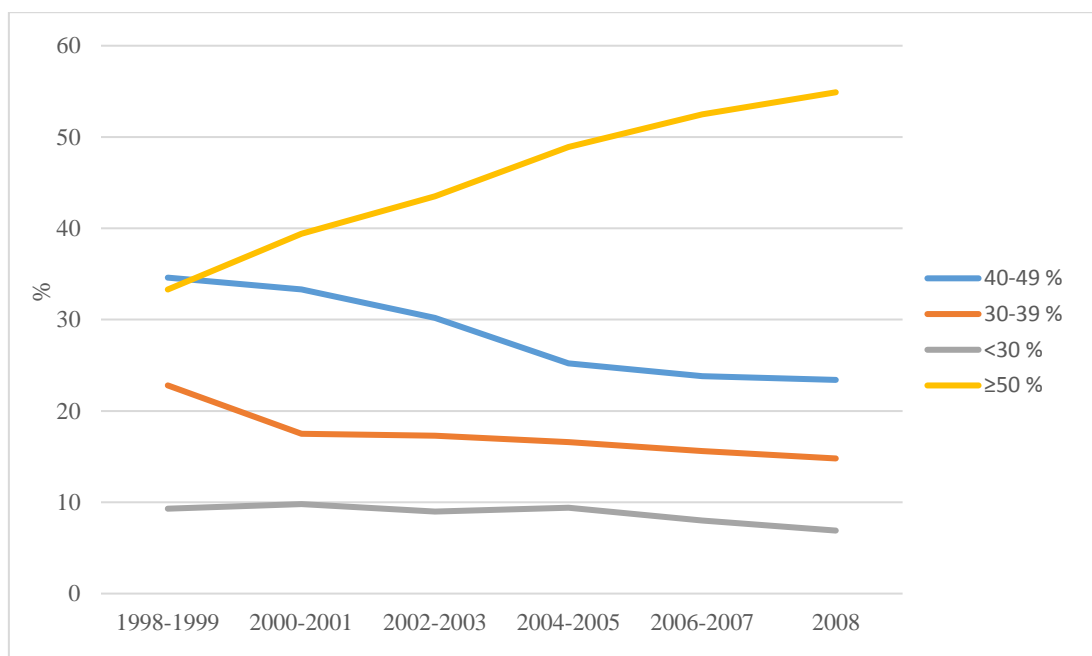
**Figure 8:** The incidence of in-hospital HF per 2 calendar year intervals between 1996 to 2008

This decrease in clinical HF was more pronounced in STEMI (from 50% to 28%) patients compared to N-STEMI patients (from 42% to 28%),  $p < 0.001$ .



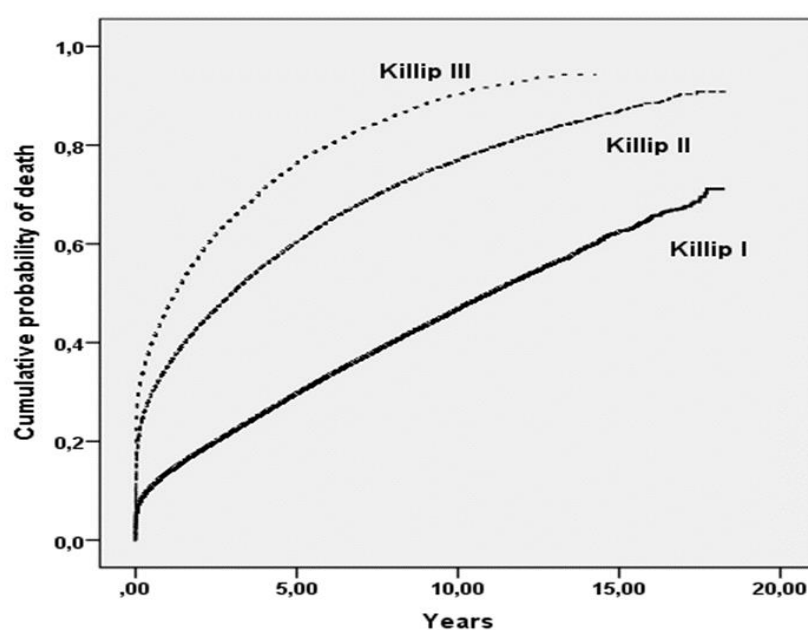
**Figure 9:** Trends in the incidence of in-hospital HF by type of MI (STEMI vs N-STEMI)

Among patients with in-hospital HF, STEMI patients constituted the majority between 1996-1997 (55.4% STEMI vs. 44.6% N-STEMI) while N-STEMI patients constituted the majority in 2008 (35.7% STEMI vs. 64.3% N-STEMI), (Figure 9).



**Figure 10:** Temporal trend in LV dysfunction (LVEF) over the years in the SWEDHEART population

The proportion of patients with signs of LV-dysfunction declined over the years while more patients were discharged with normal LVEF after the index admission in the later years (Figure 10). The proportion of HF patients with normal LVEF ( $EF \geq 50\%$ ) increased from 18% during 1998-1999 to 30% in 2008, whereas the proportion of patients with  $LVEF < 40\%$  decreased from 48% to 44%. Higher Killip class was associated with a higher long-term mortality (Figure 11). With Killip I as a reference (HR 1,0): HR 2.5, 95% CI (2.5-2.6) for Killip II and HR 4.0, 95% CI (3.9-4.1) for Killip III. Patients with Killip IV were excluded from the analysis because of their small number and already known dismal prognosis.



**Figure 11:** Long-term mortality by Killip classification during an index AMI. Log-rank  $p < 0.001$ .

Patients above 75 years of age constituted the majority of patients with in-hospital HF during the index admission followed by patients 50-75 years of age and  $< 50$  years of age respectively with a declining incidence of in-hospital HF in both sexes and all age groups.

Multivariable analysis showed that increasing age and female gender increased the odds of in-hospital HF while calendar year decreased the odds. Risk factors for in-hospital HF during hospitalization for an index AMI included history of previous MI, diabetes mellitus, hypertension, chronic kidney disease (CKD) and history of known HF.

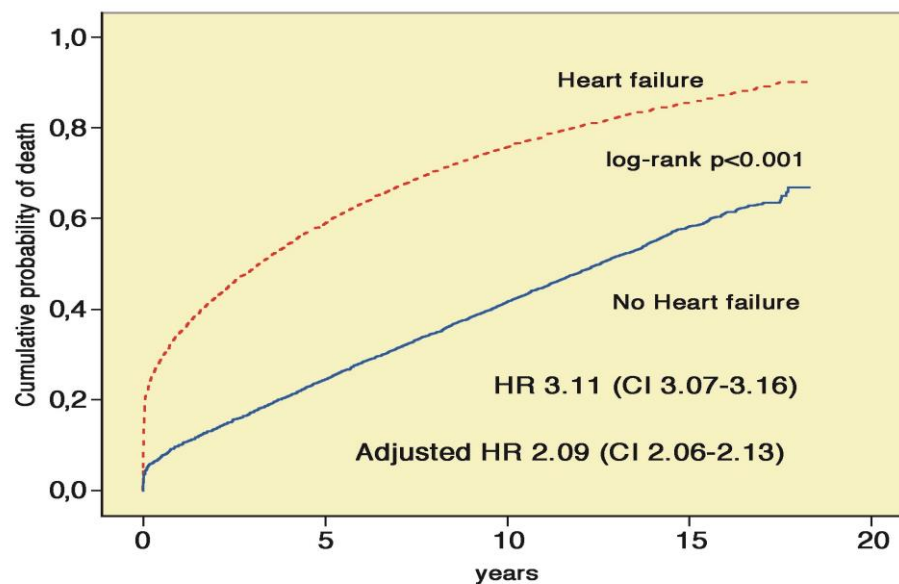
The use of PCI showed a progressive increase in both STEMI/LBBB and NSTEMI patients while the proportion of patients who were revascularized by acute CABG remained relatively unchanged (0.1% vs 0.2%). In STEMI/LBBB patients, the use of reperfusion therapy increased progressively- the majority receiving PCI treatment and a tiny proportion receiving thrombolysis in the later years of the study period. The use of

evidence-based secondary prevention pharmacologic treatment showed a progressive increase across the study period.

The estimated in-hospital, 30-day and 1-year mortality for patients with clinical HF and AMI showed a decline across the study period, (P-value <0.001).

The 1- year risk of death in patients with in-hospital HF after AMI decreased by 7% per 2 calendar years between 1996 and 2008 (OR 0.93, CI 0.92-0.94), independent of age, gender and co-morbidities. Women had a 10% lower mortality than men (OR 0.9, CI 0.8-0.91).

Long term survival analysis showed a higher mortality for patients with HF compared to those without HF (adjusted HR 2.09, CI 2.06-2.13). (Figure 12)



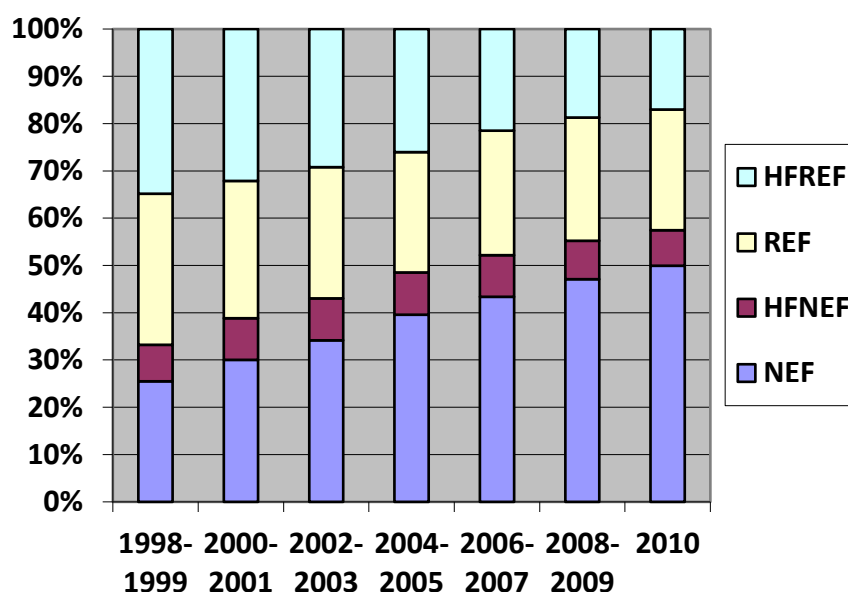
**Figure 12:** Long-Term Mortality in Patients with and without post-MI HF, *Am Coll Cardiol HF* 2015;3:234–42. Reprinted courtesy of Elsevier.

## 4.2 PAPER II

Among all AMI patients enrolled in the SWEDHEART registry for the first time between 1998-2010, data on LVEF was available in 90,320 patients. Echocardiography (99.6%) or LV angiography (0.4%) assessments generated these data. Utilization of echocardiography increased progressively over time. Patients with known and unknown LVEF were compared for differences in baseline characteristics. Patients with unknown LVEF had a higher median age (74 years versus 70 years) and the proportion of females was higher (38.2% versus 34.1%) compared to patients with known LVEF. Comorbidities were more prevalent in the

group with unknown LVEF. Patients with unknown EF had higher in-hospital (12.4% vs. 3.4%), 30-day (14.4% vs. 4.5%) and 1-year mortalities (24.6% vs.10.9%).

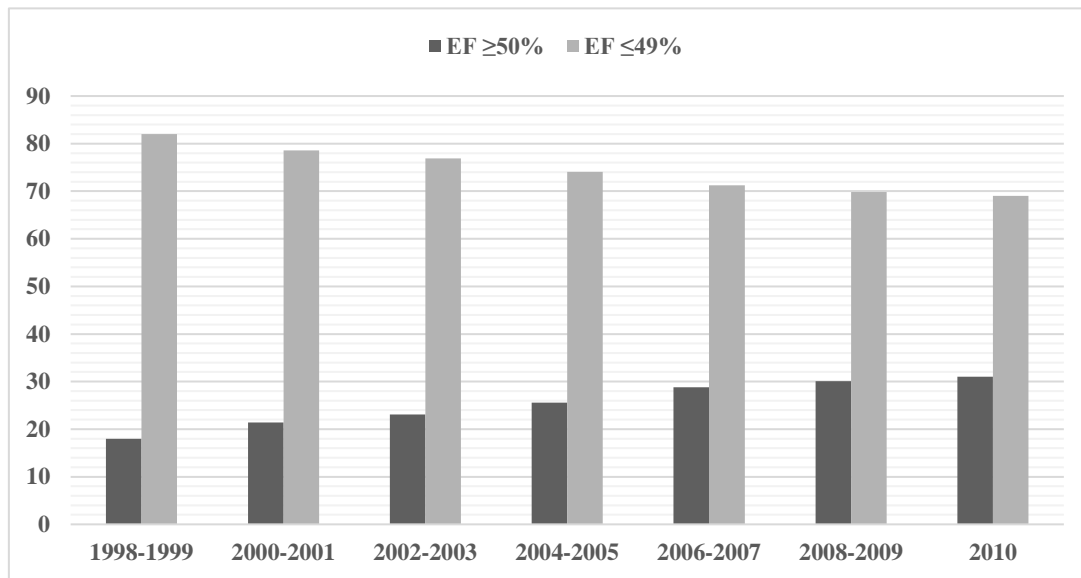
Patients with HF were older (73.3 for patients with HFNEF and 74.4 for patients with HFREF) compared to patients without HF irrespective of EF (65.7 years for NEF, 69,1 years for REF). The proportion of females was higher among HFNEF patients compared to HFREF patients (47% versus 37.5%). Hypertension was more prevalent in HFNEF patients compared to HFREF patients: 51.4% versus 43%. Newly diagnosed AF was present among 10.3% of HFNEF and 12.9% of HFREF patients. NSTEMI was more common in HFNEF patients compared to HFREF patients: 65.7% versus 50.5%. Co-morbidities such as prior MI, previous HF, prior stroke, and renal failure were more prevalent in HFNEF and HFREF patients, with slightly higher proportions in HFREF patients (except for COPD which was more prevalent in HFNEF patients). The use of reperfusion treatment in patients with STEMI or left bundle branch block was lower in HFNEF and HFREF patients, compared to patients without clinical HF – irrespective of EF.



**Figure 13:** Changes in the proportion of AMI patients by LV function and presence or absence of HF over the years, Adapted and used with permission from Eur J of Heart Failure (2016) 18,46–53<sup>210</sup>



Analysis of the study population by pattern of LV function coupled with presence or absence of clinical HF for each 2-calendar year interval between 1998-2010 showed that HFREF decreased from 34.8 % to 17% REF with no HF decreased from 32% to 25.5 %, HFNEF remained unchanged (8 %), while NEF without HF increased from 25,5 % to 49,9 % between 1998-2010 (Figure 13). Among patients with in-hospital HF, incidence of HFNEF increased from 18 % to 31 % while that of HFREF decreased from 82 % to 69 % (Figure 14).

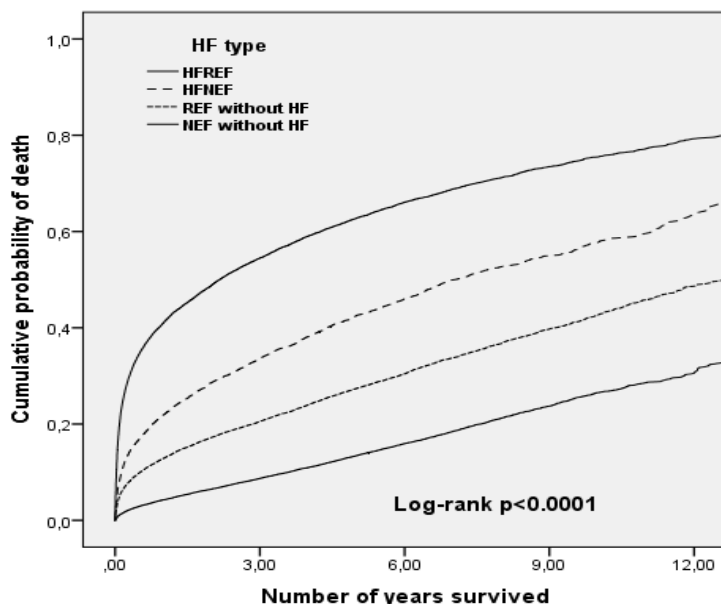


**Figure 14:** Temporal trends in incidence of clinical HF by LVEF category over the years.

**Table 3: Independent predictors of HFNEF in a logistic regression multivariable analysis model**

	Odds ratio	P-value
<b>Calendar year (2-year interval)</b>	0.88(0.85–0.9)	<0.001
<b>Age (year)</b>	1.05 (1.04–1.05)	<0.001
<b>Gender (F/M)</b>	1.3(1.2–1.4)	<0.001
<b>Hypertension</b>	1.16(1.1–1.2)	<0.001
<b>Diabetes</b>	1.6(1.5–1.7)	<0.001
<b>Atrial fibrillation</b>	3.2(2.8–3.6)	<0.001
<b>COPD</b>	2.1(1.9–2.2)	<0.001
<b>CKD (eGFR &lt;60 ml/min)</b>	1.8(1.7–1.9)	<0.001

Compared to patients with NEF without HF (reference) patients with HFNEF and HFREF showed a worse long-term prognosis. HNEF was associated with a higher long-term mortality compared to patients with LVSD (REF) without HF (Figure 15).

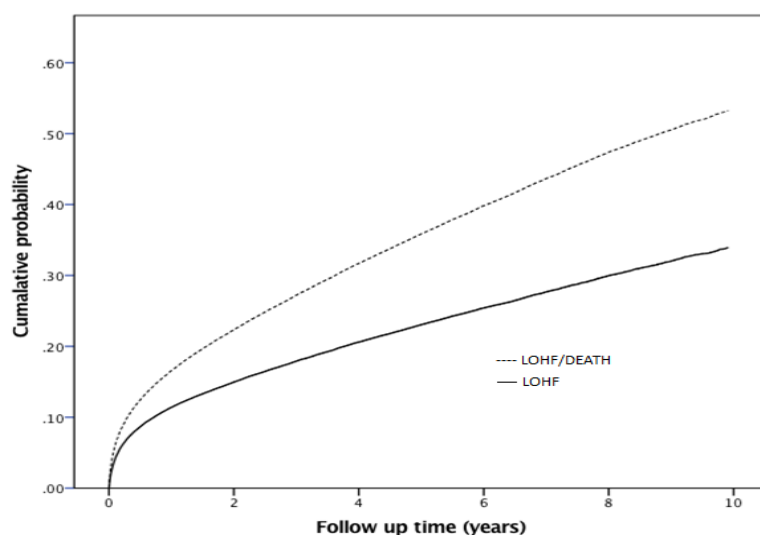


**Figure 15:** Long-term prognosis by LVEF/HF status with their respective hazard ratios: NEF [1.0], REF no HF (2.2 [2.1-2.3]), HFNEF (3.6 [3.5-3.8]), HFREF (6.9 [6.7-7.1]). Used with permission from Eur J of Heart Failure (2016) 18,46–53<sup>210</sup>

### 4.3 PAPER III

Out of 150,566 AMI survivors without prior HF, 19.4% (n=29,194) were readmitted with HF as primary or secondary diagnosis during the study period. Baseline characteristics differed significantly among patients who had HF readmission and those who did not. Patients with LOHF/death were older, more often women and with higher burden of comorbidities such as DM, hypertension and CKD compared to patients who did not develop late-onset HF. In-hospital HF was more prevalent in patients with LOHF. The utilization of statins, PCI and CABG was lower in those who developed LOHF during the study period compared to those who did not develop LOHF (Table I, paper III).

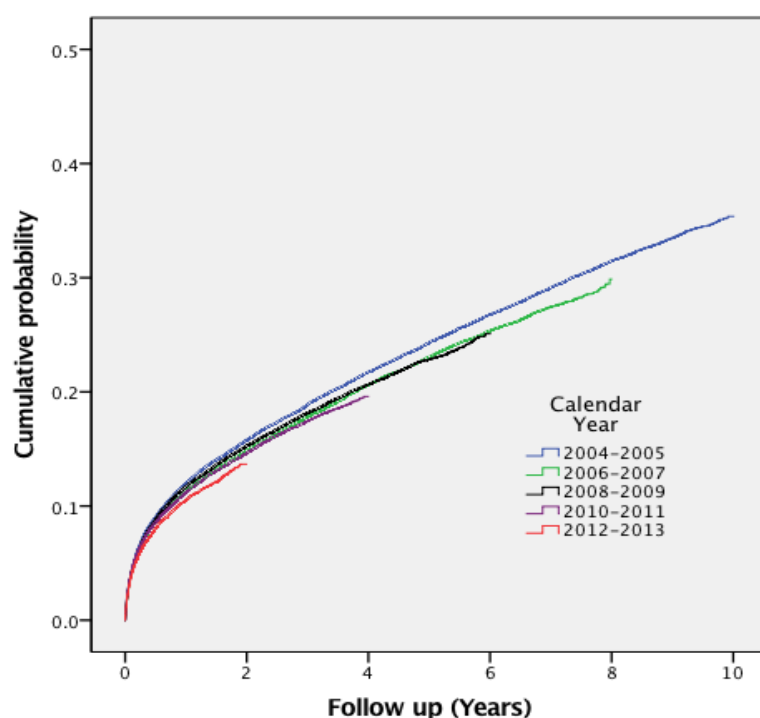
Risk profile of patients changed across the study period comparing the cohorts of 2004-2005 and 2012-2013 with decreasing prevalence of CKD (31.9% vs. 24.1%), prior stroke (9.4% vs. 7.6%), prior AMI (16% vs. 8.5%), and in-hospital HF (31.3% vs. 18.7%), while the proportion of hypertension (40.5% vs. 49.5%), COPD (4.9% vs. 6.4%) and NSTEMI (59.4% vs. 65.8%) increased and the prevalence of DM (21.1% vs. 21.5%) remained relatively unchanged. The utilization of revascularization treatment and evidence based pharmacologic treatments increased.



**Figure 16:** The risk of late-onset HF and the composite event of late-onset HF/death over 10 year period

Increasing number of known co-morbidities was associated with a higher risk of LOHF. Compared to patients who had no identified risk factors, the risk of LOHF after AMI increased by increasing number of comorbidities: with one risk factor, HR 1.9 (CI 1.9-2.05), with 2 risk factors, HR 3.3, (CI 3.1-3.4), with 3 or more risk factors, HR 5.5, CI (5.3-5.7), p-value <0.001.

The cumulative risk of developing LOHF at 1-year, 2- year and 5-year were 11.4%, 14.6% and 21.8% respectively. The corresponding figures for the composite event of LOHF/death were 16.6%, 22.4% and 35.8% respectively (Figure 16). The risk of developing LOHF within 2 years after discharge decreased from 15.5% to 14.4% between the cohorts included in 2004-2005 and 2010-2011, p <0.001 (Figure 17).

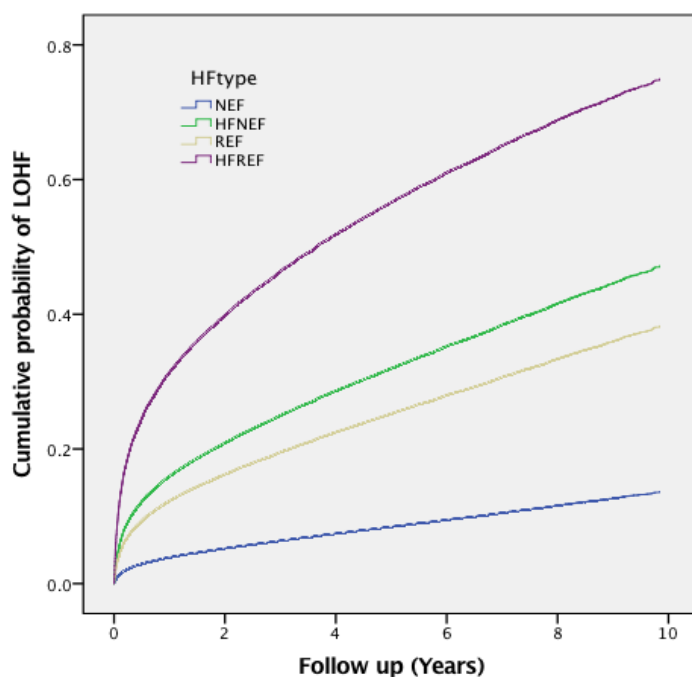


**Figure 17:** The 2-year risk of LOHF by 2 calendar-year interval: Reference 2012-13; for 2004-05 HR 1.2 (95% CI 1.1-1.2) for 2006-07, HR 1.1 (95% CI 1.04-1.1), for 2008-09 HR 1.09 (95%CI 1.01-1.2) and for 2010-11 HR 1.06, (95% CI 1.01-1.1)

The risk of LOHF showed a declining trend over the study period (2004-2005 vs. 2012-2013) after adjustment for baseline characteristics and clinical factors such as in-hospital HF, atrial fibrillation and type of AMI (STEMI/NSTEMI).

Increasing age, male gender and STEMI were associated with an increased risk of LOHF. In-hospital HF increased risk of LOHF by 2-3-fold. Comorbidities increased the risk of LOHF significantly. Calendar year was associated with a lower risk of LOHF/death.

Compared to patients with NEF without HF, the risk of HF readmission was much higher for patients with HFNEF (by four to five-fold) and patients with HFREF (by almost ten-fold). Patients with HFNEF showed a higher risk of HF readmission compared to patients with REF without HF ( $p < 0.001$ ) (Figure 18).



**Figure 18:** The risk of late-onset HF by LVEF/HF status HF: Reference NEF without HF: HR 9.5, (CI 9.1-9.8) for HFREF, HR 4.3 (CI 4.1-4.6) for HFNEF, HR 3.3 (CI 3.2-3.4) for REF without HF.

#### 4.4 PAPER IV

Between October 2005 and December 2010, 71,638 patients with their first AMI were enrolled in the registry. After excluding patients who died in-hospital, with previous history of HF and with unknown LVEF a total of 40,697 patients remained for the final analysis. The proportion of patients by status of in-hospital HF and LVEF categories were: NEF without HF in 55.1% (n=22,405), REF without HF in 25.7 % (n=10,481), HFNEF in 7.6 % (n=3,082) and HFREF in 11.6 % (n=4,729). Patients with HFNEF and HFREF were older. The highest proportion of women was seen in patients with HFNEF. Comorbidities such as diabetes,

hypertension, CKD were more prevalent in patients with HFNEF and HFREF compared to REF and NEF. At time of admission, 25.6 % of all AMI patients were already on beta-blockers.

Beta-blockers were prescribed to 90.7% (n=36,869) of all AMI patients at discharge. Patients with REF without HF and HFREF were more likely to receive beta-blockers during discharge, while patients with HFNEF were less likely to receive treatment with beta-blockers compared to patients with NEF without HF. The likelihood of beta-blocker prescription was higher in patients with REF compared to patients with HFREF. These findings were consistent after adjustment for potential contraindications for beta-blockers (Model 1).

Among one year survivor AMI patients, 68,9% (n=26,595) reached the threshold level for adherence ( $PDC \geq 80\%$ ) for long-term beta-blocker treatment. Compared to patients with NEF without HF, patients with REF without HF were more likely to reach the adherence level. Patients with HFNEF were less likely to reach the threshold for adherence.

Multivariable analysis showed that socioeconomic factors such as being married/cohabiting, higher educational level and clinical factors such as hypertension, STEMI and revascularization treatments (PCI and CABG) were associated with better adherence to beta-blocker drugs while higher odds of non-adherence was seen in patients with increasing age, low income level, non-married/non-cohabiting, COPD, prior stroke, prior cancer, bleeding, dementia, peripheral arterial disease and being on dialysis treatment as well as known relative contraindications such as heart rate  $<60/\text{min}$  and high grade AV-block during hospitalization.

The 2-year and 4-year cumulative risks for the composite of LOHF or death were lower for patients who were adherent to beta-blocker treatment compared to patients who were non-adherent (5.4% vs. 8.5% and 13.8% vs. 20.3% respectively). Patients with both HF and LVSD (HFREF) showed the highest cumulative risks in both groups followed by patients with HFNEF, REF without HF and NEF without HF respectively.

Adherence to beta-blocker treatment was associated with a reduction in all-cause mortality and the composite of LOHF/death in both the crude and adjusted analysis in all AMI patients. These findings remained consistent even in the subgroup analysis with the exception of patients with HFNEF where statistical significance was not reached in the adjusted analysis though a trend towards favourable association was seen (Table 4). Interaction tests showed significant p-values ( $<0.05$ ) for all cause-mortality and non-significant p-values ( $>0.05$ ) for the composite end-point indicating that the association between adherence to beta-blocker

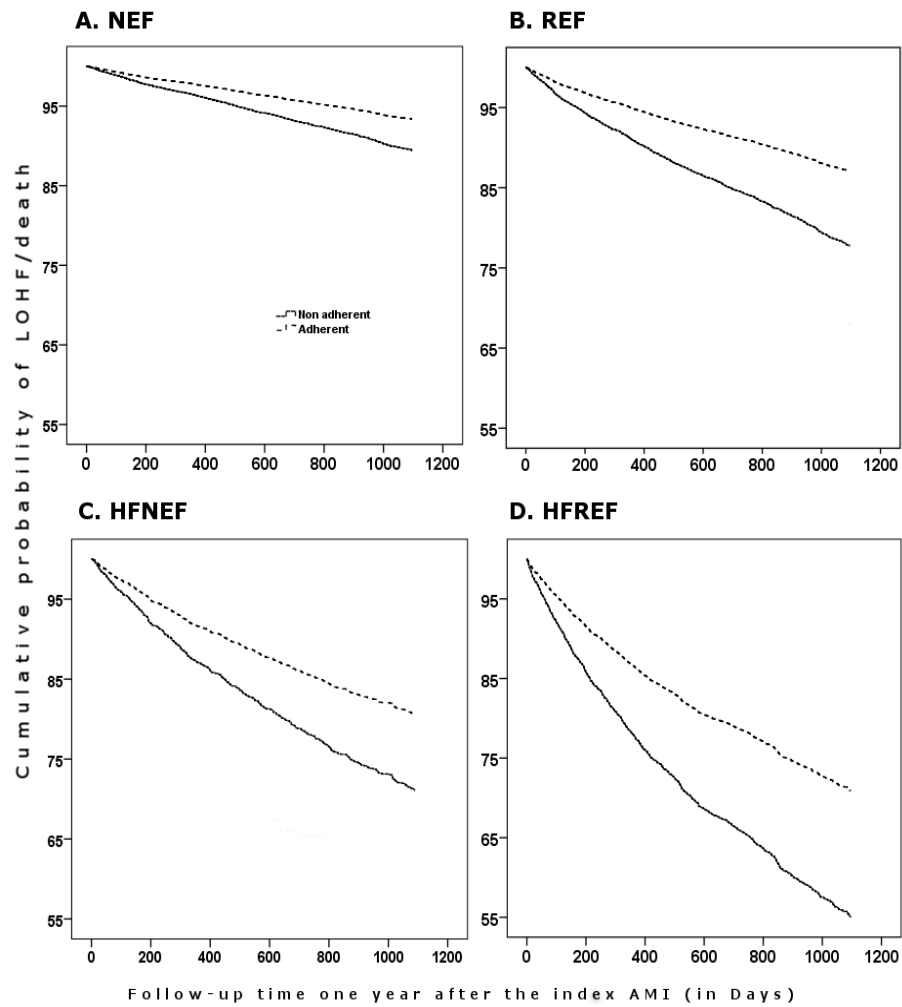
treatment and all-cause mortality does differ between the LVEF subgroups (normal LVEF vs reduced LVEF irrespective of status of HF).

Long-term survival analysis showed favourable prognostic associations between adherence to beta-blocker treatment and the long-term risk of LOHF/death for all LVEF/HF as shown by survival curves that continue to diverge after 3 years (Figure 19A-D).

**Table 4: Adherence to beta-blockers among one year survivors of AMI and associations with all-cause mortality and the composite of LOHF/all-cause mortality**

	All patients	NEF	REF	HFNEF	HFREF
<b>Death</b>					
Crude	0.55 (0.52-0.66)	0.62 (0.55-0.69)	0.49 (0.43-0.55)	0.59 (0.49-0.71)	0.50 (0.44-0.57)
Adjusted	0.79 (0.73-0.85)	0.84 (0.75-0.95)	0.70 (0.61-0.80)	0.90 (0.74-1.10)	0.73 (0.63-0.85)
<b>Combined</b>					
Crude	0.65 (0.62-0.69)	0.66 (0.60-0.73)	0.59 (0.54-0.65)	0.63 (0.55-0.73)	0.66 (0.59-0.73)
Adjusted	0.86 (0.81-0.91)	0.88 (0.80-0.98)	0.77 (0.69-0.85)	0.86 (0.74-1.02)	0.87 (0.78-0.98)

Combined = LOHF or death; Adjustments were made for: age, sex, diabetes, hypertension, CKD, prior stroke and drugs (ASA, ACE/ARB, Statins, B-blocker on admission), performed PCI or CABG during hospitalization, other antiplatelet/anticoagulant at discharge, and adherence to other drugs during first year (ASA, ACE/ARB, statins).



**Figure 19A-D:** Long-term risk of LOHF/death for the four LVEF/HF categories by status of adherence to beta-blocker treatment

## 5 GENERAL DISCUSSION

### 5.1 MAJOR FINDINGS

The incidence of acute post MI HF decreased by 39% (an absolute risk reduction of 18%) over the study period with more pronounced reduction among patients with STEMI (ARR 22%) than N-STEMI (ARR 14%).

Despite declines in the incidence of HF complicating acute MI with declining in-hospital, 30-day, and 1-year mortality, HF was associated with a 2-fold greater risk for death in the long-term compared with patients without HF after AMI. Simply put, we learned that if and when HF complicates acute MI, even if manifested only by basilar rales, prognosis worsens markedly.

HF with normal EF is relatively less common in the setting of AMI. However, the proportion of patients with HFNEF increased from 18% to 31% among patients with in-hospital HF mainly due to a decline in the incidence of LVSD without HF and HFREF. Patients with HFNEF were more likely to have more comorbidities compared to patients without HF irrespective of EF.

The occurrence of HFNEF carries a poor short- and long-term prognosis with at least a three-fold increase in long-term all-cause mortality compared to patients without HF irrespective of LVEF. Among AMI patients with clinical HF, the ones with the highest risk of mortality are those who exhibit evidence of both HF and LVSD, i.e. patients with HFREF.

LOHF is a common late complication after AMI occurring in almost one out of five AMI patients within 5 years after discharge with certain risk for underestimation given the methodology we used for case ascertainment. Patients with LOHF were older and with a higher burden of comorbidities. Increasing burden of comorbidities was associated with higher risk of LOHF. The crude overall risk of LOHF shows a small but clearly decreasing trend after an index AMI over time which seems to be related to a decreasing burden of comorbidities and an improved acute treatment.

The prescription of beta-blockers after AMI is high in Sweden with close to 91% of AMI patients receiving prescription during discharge from the index admission. However, nearly one out of three one year survivors were non-adherent to beta-blocker treatment one year after the index AMI.

Patients with REF and no signs of HF and HFREF were more likely to receive beta-blockers at discharge in our cohort which is encouraging and in line with guideline recommendations.



Patients who did not develop HF and had normal LVEF during hospitalization were more likely to discontinue beta-blockers at 1 year while patients with REF had the highest likelihood to adhere to beta-blocker treatment.

Adherence to beta-blocker treatment was associated with improved long-term outcomes in AMI patients except in patients with HFNEF. The favorable long-term prognostic effect in patients with NEF without HF is of particular interest and challenges the lingering uncertainty regarding the indication for long-term treatment beta-blocker treatment after AMI in low-risk patients.

### **5.1.1 In-hospital post-infarction HF**

Over the last several decades, important changes have taken place in the epidemiology of MI. Population studies have shown declining burden of the coronary risk factors such as total cholesterol, blood pressure and tobacco smoking, while diabetes and BMI increased significantly with a net reduction in risk factors which subsequently is reflected by a decline in the incidence and case-fatality rate of AMI <sup>136</sup>. Besides, a number of advances in cardiovascular medicine have conferred reduced mortality for patients with AMI over the past 50 years. The advent of the coronary care unit has afforded specialized care with possibilities for lifesaving monitoring. Reperfusion therapy has led to reductions in infarct size and mortality, and several medications have been shown to be lifesaving. All these factors have likely influenced the already complex and multifaceted association between HF after MI and mortality.

Changes have also occurred in the epidemiology of HF after MI, with a decline in its incidence and a change in the case mix according to left ventricular dysfunction, characterized by an increasing proportion of HF cases presenting with HFPEF, for which treatment benefits are less established <sup>193</sup>.

It is also highly likely that improvements in the treatment of AMI have led to a larger number of survivors. In survivors of AMI, these treatments result in a reduction in the extent of myocardial injury and greater myocardial salvage. To the contrary, others who could have died previously may now survive, but with significant myocardial damage. The net consequences of these effects on the risk of early and late-onset HF after AMI is uncertain <sup>211</sup>. The findings of Paper I reflect most probably the net effect of all the advances mentioned above and changes in patient characteristics over the years and are consistent with those of other recent studies <sup>96, 212-214</sup>.

Over the years, the diagnostic criteria for AMI has changed, with increasingly sensitive biomarkers being used in the later years. Many patients diagnosed to have AMI to date were previously diagnosed as unstable angina. Although the incidence rates of AMI and subsequent post-MI HF has probably been altered by the use of sensitive biomarkers, the decline in the incidence of HF in our study showed a rather smooth progressive decline, suggesting other explanations, such as more frequent use of effective evidence-based treatments and changes in the burden of risk factors. The larger decline of HF in STEMI patients as compared to patients with NSTEMIs also speaks for a true overall temporal decline in the incidence of HF after AMI. Thus, the decline in post MI HF observed in our study could be a reflection of changes in ascertainment of AMI, decreased severity on presentation, as well as advances in the management of AMI<sup>215</sup>. These evolutions in determinants of the incidence and prognosis of HF after MI point to the need for the continuous assessment of contemporary trends of post MI HF and its current prognostic role. It appears that previous estimates are now outdated because they do not reflect the aforementioned changes in the epidemiology of MI, and HF complicating MI, in the population.

### **5.1.2 HF with normal EF in the setting of AMI**

Heart failure and LVSD are not synonymous<sup>181</sup>. Some patients will remain asymptomatic despite suffering major left ventricular damage. Previous studies reported that 30-50% of patients who develop HF will do so without LVSD, mitral regurgitation, or arrhythmias<sup>82, 148</sup>. While LVSD is assessed objectively, the diagnosis of HF remains subjective with varying threshold for diagnosis among physicians. Both LVSD and HF may occur early or develop late and both may recover<sup>186-188</sup>.

The findings of Paper II showed that evidence of HFNEF was present in a proportion of AMI and when it occurred was associated with poor short-term, intermediate and long-term prognosis though slightly better than patients with HFREF.

Several studies have shown that Killip class and reduced LVEF are predictors of poor long-term outcome<sup>153, 173, 177, 182-184</sup> which is consistent with the findings of our study. The pathogenesis of HFNEF after AMI is not well described. Activation of cardiac peptides<sup>216</sup> and the RAS has been suggested as contributors<sup>217</sup>. Studies have shown doppler echocardiographic signs of elevated filling pressures in these patients<sup>218</sup>.

Paper II also showed a higher burden of comorbidities such as hypertension, diabetes and other atherosclerotic manifestations in patients with HFNEF compared to patients that did not

develop in-hospital HF after AMI. As cardiovascular disease is suggested to be a continuum of events<sup>219</sup>, the increased burden of comorbidities might eventually progress to overt CAD with increased susceptibility to an acute loss of even relatively small amounts of cardiac muscle and subsequent development of HF.

As the optimal management of these patients is not known, mechanistic studies that shed light on new insights in the pathophysiology and therapies of this distinct phenotype of HF are warranted.

The coexistence of clinical signs of HF and LVSD (HFREF) is associated with the worst long-term prognosis. Although with better long-term prognosis compared to patients with patients with HFREF and HFNEF, our study confirmed also a substantially increased long-term mortality in patients with LVSD without signs of HF. This finding confirms the findings of previous studies<sup>150, 181, 182</sup>. As evidence-based treatment is available for these group of patients, early identification, triaging and initiation of pharmacologic and device therapies as appropriate improves their long-term prognostic outlook.

### **5.1.3 Long-term risk of HF after AMI**

Besides heightened risk of mortality, other major non-fatal cardiovascular events such as recurrent MI, arrhythmia, stroke, and HF occur more frequently among survivors of the acute event. However, the risk for cardiovascular events among MI survivors is not uniform.

Factors such as the patient's baseline characteristics, infarct extent and complications as well as the use of medications and procedures, have been shown to influence prognosis<sup>101, 102</sup>.

The occurrence of LVSD with or without HF after AMI depends on factors, such as recurrent myocardial ischemia, infarct size, ventricular remodeling, stunned myocardium, mechanical complications and hibernating myocardium<sup>162, 185</sup>. While in-hospital HF is usually related to infarct size, mechanical complications, or myocardial stunning, the development of late-onset HF is mainly related to progressive myocyte loss, hibernating myocardium, and ventricular remodeling<sup>220</sup>.

Our study showed that LOHF was a common late complication after AMI. Patients with in-hospital HFREF had the highest risk of LOHF/death followed by patients with HFNEF and REF without HF respectively. Independent predictors of HF include in-hospital HF, increasing age, history of hypertension, history of prior MI, and diabetes. Although the utilization of revascularization treatment and pharmacologic treatments in AMI patients improved over time, their use was lower among patients who developed LOHF during

follow up. Similar findings have been reported by previous studies<sup>175</sup>. This is particularly of concern as these treatments have been shown to improve long-term outcomes significantly<sup>174, 221, 222</sup>. The explanations behind the underutilization of potentially life-saving treatments in this group of patients are not well described and could be multifactorial. Advanced age, concern for potential side effects such as hypotension and worsening renal failure or unawareness of current standards of care, or non-clinical factors such as patient gender or geographic limitations to timely access optimal treatment could be among the reasons that may impact management decisions.

LOHF after MI is a serious complication because of a several-fold increase in the risk of death<sup>56, 101, 102</sup>. Hence, a better understanding of the predictors of LOHF in long-term MI survivors would be helpful to identify high-risk patients more likely to benefit from implementation of more aggressive preventive measures. The importance of optimizing the availability and effective utilization of such strategies in high risk patients need to be underscored.

The mainstay of HF therapy today remains reactive treatment for established and symptomatic disease. However, the burden of HF on our societies will continue to grow until effective primary and secondary prevention strategies are adopted and employed, along with increased awareness of lifestyle choices that can modify risk factors for developing HF<sup>223</sup>. This is the basis of the staging concept of HF. Hence, our finding underscores the importance of identifying at risk patients and treating them aggressively to prevent the development of HF by preventing overt CAD and subsequent MI<sup>224</sup>.

#### **5.1.4 Adherence to beta-blockers post AMI and effect on prognosis**

Clinical trials have demonstrated that selected pharmacotherapies reduce cardiovascular mortality<sup>225, 226</sup>. How their projected survival impact real-world patients is less known, in part because of variations in drug adherence. Quality improvement initiatives have mainly focused to improve inpatient administration of appropriate drugs during hospitalization for the index AMI at hospital discharge.

Studies have demonstrated the association between better adherence and long-term clinical outcomes among patients hospitalized with acute coronary syndromes<sup>227, 228</sup>.

While in general pharmacologic non-adherence could be deemed as a risk for unfavourable outcome, whether it applies to patients who receive beta-blocker drugs without strong evidence supporting it is unknown. Patients with NEF without HF and patients with HFNEF

belong to such a category. It is unclear if non-adherence to beta-blocker treatment in those patients implied increased risk for poor long-term outcomes making it difficult to make proper judgment.

Our study showed that adherence to beta-blocker treatment was associated with improved long-term outcomes in all AMI patients except in patients with HFNEF. Similar findings have been reported by previous studies<sup>227-230</sup>. The favorable long-term prognostic effect in patients with NEF without HF is of particular interest and challenges the uncertainty regarding the indication for long-term treatment in this subset of patients and calls for well-designed randomized trials to address the ambiguity.

The role of adherence to drug specific effects on long-term survival benefits has been questioned, in part because prognostic benefits may be the result of "healthy adherer" behavioral factors more so than to specific pharmacological benefits<sup>231</sup>. Yet, other investigators have reported findings that demonstrated the importance of class-specific drug effects as mediators of favorable long-term prognostic implications of better adherence beyond the "healthy adherer" behavioral attributes<sup>232</sup>.

Non-adherence is also related to increased risk of hospitalization and cost<sup>233</sup>. Hence, given the huge impact of HF readmissions both on patients as well as health care systems, working on strategies that ensure better adherence to beta-blocker treatment and other secondary prevention therapies could contribute towards better outcomes that includes HF related events.

## **5.2 GENDER DIFFERENCES**

Paper I showed that the incidence of in-hospital post MI HF is approximately one-third lower for women than men. As in previous studies, women who suffer from a MI showed a higher risk of developing HF than men<sup>97</sup>. However, their long-term prognosis seems to be better than their male counterparts. Post MI HF showed an increasing trend among women over the years. Their relative proportion was also higher among patients with HFNEF. Female gender was strong predictor of HFNEF together with comorbidities such as diabetes mellitus, hypertension, AF, and chronic kidney disease. Women were less likely than men to undergo measurement of left ventricular function as the group with unknown LVEF was overrepresented by elderly patients who are more often women and with higher burden of comorbidities. Previous studies have shown underutilization of appropriate diagnostics particularly in women which in turn could lead to undertreatment as most studies on the treatment of HF include only patients with REF<sup>234</sup>.

Patients with LOHF and those with LOHF or death were older, more often women and with higher burden of comorbidities. However, female gender was associated with a lower risk of LOHF and the composite event of LOHF/death after adjustment for background factors. There was no statistically significant gender difference with regards to adherence to beta-blocker treatment.

Women have been hugely underrepresented in HF trials of left ventricular dysfunction with the proportion of randomized patients in the major trials ranging from 0% to 32%<sup>97</sup>. Nearly half of the population hospitalized with HF constitute HF with preserved EF. With women having more often HF with preserved EF than men, less CAD as the underlying cause of their HF, being older and exhibiting hypertension, diabetes and AF<sup>235</sup>, improvement in survival in women with HF might be expected to be less marked than men. Most studies on the treatment of HF include only patients with HFREF largely excluding patients with HFPEF<sup>234</sup>.

Although women have a lower incidence of HF after AMI, their proportion is increasing steadily warranting a special attention especially in future studies that elucidate pathophysiologic insights and novel therapeutic strategies.

### **5.3 MONITORING OF TRENDS IN POST-MI HF**

As cardiovascular disease is regarded as a continuum of events<sup>219</sup>, AMI patients both with and without in-hospital HF have a higher risk of developing chronic heart failure and death. With improved MI management and medical therapy to combat neurohormonal activation, HF now spans a wide spectrum of disease, ranging from acute decompensation to a chronic asymptomatic state. Our findings highlight the fact that HF after AMI is still a common occurrence and we will continue to see this complication despite the changes in the epidemiology of acute coronary syndromes.

Given the magnitude of AMI and evolving approaches to manage it, continued monitoring of these trends remains of considerable clinical and public health importance. Moreover, readmissions because of HF are common and remain the main driving factor to the huge economic burden related to HF. Thus, studying readmission rates related to HF after AMI and predictors of late-onset HF after AMI is of crucial importance.

## **5.4 LIMITATIONS**

### **5.4.1 Overall limitations**

In observational studies one cannot rule out the possibility of selection bias and residual confounding. It is important to be aware that the register does not include the entire AMI population<sup>236</sup>. Elderly AMI patients with multiple comorbidities and mostly female are likely to receive care outside of CCUs and hence not be included in the registry. This circumstance decreases the external validity of our findings<sup>237</sup>.

A proportion of the patients in the studies have missing data on some of the variables. Patients with missing data are known to have higher mortality and, therefore, their exclusion from analyses might have produced biased results. All analyses are performed with complete cases and imputations were not performed. However, imputations performed in other studies based on the SWEDEHEART register has not showed a different result from the primary analyses and therefore we don't believe this would be a major limitation. In paper I, we presented the number of patients included in the analysis for most of the variables. In paper II, we summarized characteristics of patients with missing LVEF data and presented differences compared to the study population. Lastly, in all papers, several statistical tests were used, which increases the risk of associations occurring by chance.

### **5.4.2 Paper I**

A clinical definition of HF was used to identify patients with in-hospital HF which has its own limitation due to the non-specific nature of physical findings. However, pulmonary rales in the setting of AMI are shown to have high sensitivity to predict an unfavourable hemodynamic state and worse outcomes<sup>176, 177</sup>. A similar definition was used by other studies<sup>166, 173, 238</sup>. Moreover, our criteria also included the use of IV diuretic agents or IV inotropes which increases sensitivity but may also lower specificity. HF at admission could not be distinguished from HF which develops during hospital stay restricting the possibility to further explore differences in clinical characteristics and outcome.

### **5.4.3 Paper II**

The diagnosis of HF based on any criteria is prone to misclassification. It is obvious that dyspnea and pulmonary findings could be explained by other cardiovascular and non-cardiovascular factors such as obesity and COPD. This may hold true for some patients in the present study. COPD was seen more often among patients with HFNEF than patients without

HF. However, more than 85% of patients with HFNEF did not have any history of COPD, suggesting misclassification was not a major problem.

Although LVEF may be reduced in the acute setting, it recovers in a substantial proportion of patients within a few months. As HFNEF and HFREF are traditionally used in the setting of chronic HF, the use of the terms in the setting of acute HF associated with AMI could be a point of discussion. Our findings may not be generalizable to other non-hospitalized populations and hence one should be aware of differences in clinical settings. Other studies which investigated the clinical and prognostic implications of acute HF with preserved EF post AMI have also used similar approaches <sup>148</sup>.

#### **5.4.4 Paper III**

Less severe HF not requiring hospitalization could have been missed as the development of HF in this study required hospitalization, which may have contributed to a relatively lower incidence of LOHF. A hospital diagnosis of HF in Sweden has been validated against ESC criteria for the definition of HF, with 82% of the HF cases in the hospital discharge register classified as having a definite HF according to the ESC definition <sup>207</sup>. Other studies have shown administrative codes to be highly specific for cardiovascular diagnoses and risk factors <sup>239</sup>. In any case, what we risk mainly is under diagnosing HF. Hence the findings of this study remain valid with several implications in understanding the complex interaction between MI and HF.

#### **5.4.5 Paper IV**

As is true for observational studies, we are restricted to explore fully the influence of unmeasured confounders. Meanwhile, the observed effect of better adherence reinforces the findings of randomized and observational studies regarding the effect of beta-blockers after AMI on long-term outcomes.

We are also unable to account for brand, dosage administered, or continued use of drugs. As a result, this will remain an inherent limitation. It is known that dosage of beta-blockers used constitute an important aspect of beta-blocker treatment as under-dosage of beta-blockers is a common problem <sup>240, 241</sup>. Furthermore, we cannot be certain whether a patient actually took the medication despite drug refill. As drug prescription in Sweden only covers 3 months at a time, if patients do not refill, one can assume a higher possibility of discontinuation in the majority of patients.



## 6 CONCLUSIONS

- A marked decrease was found in the incidence of HF complicating AMI between 1996 and 2008. However, HF continues to worsen the early-, intermediate-, and long-term adverse prognostic risk after AMI. The observed declining trend in the incidence of HF and mortality indicates the potential for further decline with further improvements in therapeutic strategies.
- Killip classification helps identify a high-risk group for whom specific therapies need to be targeted. Patients with a higher Killip class after AMI (i.e., Killip class  $\geq$ II) likely require triage to a higher level of care to prevent adverse outcomes.
- Heart failure with NEF is a relatively less common form of HF in the setting of AMI. Nonetheless, its relative proportion is increasing and its occurrence carries a poor short- and long-term prognosis.
- Long-term survivors of MI without a previous history of HF remain at risk of late-onset HF. The risk of LOHF over time seems to show a declining trend mainly related to a decreasing burden of comorbidities and an improved treatment of AMI over time.
- The prescription of beta-blockers as secondary prevention medications after AMI is high in Sweden. However, a significant proportion of MI survivors discontinue beta-blockers one year after the index event. Patients with LVSD without HF and HFREF were more likely to receive beta-blockers at discharge. Adherence to beta-blocker treatment was associated with improved long-term outcomes except in patients with HFNEF where the effect is less obvious.

## 7 CLINICAL IMPLICATIONS

Though progress has been made in AMI treatment, the lingering problem of HF underscores the importance of prompt and effective revascularization and pharmacologic treatments to salvage myocardium at risk and inhibit the development of in-hospital HF. Although we notice encouraging trends, our findings highlight the important fact that HF after AMI is still a common occurrence and we will continue to see this complication despite the changes in the epidemiology of acute coronary syndromes.

Our findings emphasize also the benefits of LV function assessment and vigilance on clinical signs of HF to risk stratify patients after AMI as they are at higher risk of late-onset HF and death after discharge. Moreover, our findings give insight regarding the need for devising and implementing strategies that improve adherence to guideline recommended secondary prevention therapies.

## 8 FUTURE PERSPECTIVES

The epidemiology and treatment of AMI is evolving continuously. The burden of HF on society is predicted to grow underscoring the need for effective primary and secondary preventive strategies. AMI, which is the dominant precursor of HF can be prevented from occurring in most patients<sup>138</sup>. To further improve the demonstrated encouraging trends by our results, a continuous effort to identify potential areas of intervention to reduce the risk of HF after AMI is needed. First, health systems need to intensify their effort in informing and empowering citizens to adopt healthy life styles to mitigate the burden of risk factors. Second, improving access to health care that facilitates the early detection as well as initiation and optimization of effective treatment in patients with established risk factors to prevent evolution to CAD is required. Third, more effort need to be made to diagnose and treat both AMI and post MI HF earlier with existing interventions while undertaking further research to find new interventions.

The understanding of pathophysiological mechanisms has introduced several paradigms which transformed the treatment of HF over the last several decades<sup>109</sup>. However, there is still a need for a continued effort in understanding undiscovered pathophysiologic mechanisms in the different phenotypes of HF to open new doors for effective therapeutic approaches. This is particularly true in patients with HF with preserved EF and acute HF. This should go hand in hand with quality improvement initiatives for monitoring of evolving trends and the evaluation of implemented interventions to enhance the continuous development of evidence-based cardiac care.

## 9 SVENSK SAMMANFATTNING

Hjärtsvikt är en allvarlig sjukdom med 5-års överlevnad på c:a 50%. Kranskärslsjukdom är en huvudorsak till hjärtsvikt. Övergripande målet för denna avhandling är att beskriva förekomst av hjärtsvikt efter hjärtinfarkt, både som akut komplikation vid hjärtinfarkten samt som sen komplikation i form av återinläggning för hjärtsvikt eller död. Vidare analyserades tidsmässiga trender i förekomst av hjärtsvikt, förändringar i patienternas bakgrund, behandling och riskfaktorer och deras prognostiska betydelse. Dessutom, användning och följsamhet till behandling med betablockerare som sekundärprevention studerades och om bättre följsamhet gav förbättrad långtidsprognos. För avhandlingen analyserades data ur det nationella kvalitetsregistret för akut kranskärslsjukdom, SWEDHEART.

Arbete 1 studerade 199,851 hjärtinfarktpatienter inlagda för hjärtinfarkt mellan år 1996 och 2008. Arbete 2 ägnades att studera 90,320 patienter 1998 till 2010 avseende betydelsen av klinisk svikt och systolisk vänsterkammardysfunktion med fokus på hjärtsvikt med normal systolisk funktion ( $EF > 50\%$ ). Tredje arbetet studerade 150,566 patienter utan tidigare hjärtsvikt som överlevde sin hjärtinfarkt 2004 till 2013 avseende risken för framtida död eller återinläggning för hjärtsvikt och dess riskfaktorer. Sista studien beskrev 40,697 patienter år 2005-2010 och ordinerad behandling av betablockerare och följsamhet till denna året efter hjärtinfarkt i relation till förekomst av initial hjärtsvikt och hjärtfunktion samt fortsatt prognos.

Förekomsten av hjärtsvikt i samband med infarkt minskade med 39% (ARR 18%) över 13 år. Minskningen var stor både vid ST-höjnings- och icke-ST-höjnings-infarkt men var störst hos patienter med ST-höjning. Användningen av revaskularisering (PCI) och evidens-baserad farmakologisk behandling ökade under studietiden. Hos patienter som utvecklade hjärtsvikt på sjukhuset sågs sjunkande mortalitet både på sjukhuset (19% vs 17%), samt inom 30 dagar (23% vs 17%) och 1 år (35% vs 31%) mellan 1996 och 2008. De patienter som skrevs ut med påvisad hjärtsvikt på sjukhuset hade en betydligt ökad risk för död över tid jämfört med patienter utan hjärtsvikt (justerad HR: 2.09; 95% CI: 2.06 to 2.13).

Andra studien visar att hjärtsvikt med bevarad vänsterkammar EF (VKEF) är en relativt ovanlig form av hjärtsvikt i det akuta infarktsammanhanget och förekommer i c:a 8% av alla hjärtinfarktpatienter. Bland patienter som utvecklade hjärtsvikt vid infarkten ökade andelen med bevarad EF från 18% 1998–99 till 31 % 2008, tillståndet är vanligare hos äldre patienter och kvinnor. Vidare är hypertoni, diabetes, kronisk njursvikt, förmaksflimmer och KOL starka prediktorer. Hjärtsvikt med bevarad EF ökar risken för långtidsmortalitet minst 3

gångar jämfört med patienter med normal EF utan hjärtsvikt och var också associerad med betydligt högre risk jämfört med patienter med nedsatt VKEF utan klinisk svikt. Patienter med nedsatt VKEF och klinisk hjärtsvikt har sämst prognos jämfört med övriga infarktgrupper uppdelade efter VKEF och klinisk hjärtsvikt.

Hjärtinfarktpatienter har ökad risk att utveckla hjärtsvikt senare. Utav 150,566 patienter som inkluderades i SWEDHEART registret mellan 2004 och 2013 blev 19,5% (n=29,194) återinlagda på grund av hjärtsvikt någon gång efter utskrivning. Den kumulativa risken för hjärtsvikt 1 år, 2 år och 5 år efter utskrivning var 11.4%, 14.6% and 21.8%. Patienter med klinisk hjärtsvikt med nedsatt VKEF redan på sjukhuset har den största risken följt av patienter med bevarad VKEF och klinisk svikt, nedsatt VKEF utan svikt och bevarad VKEF utan svikt. Resultatet visar också sjunkande trend för återinläggning på grund av hjärtsvikt över tid vilket bedöms bero på minskat antal sam-sjukligheter och ökad användning av PCI och annan evidensbaserad farmakologisk behandling.

I fjärde arbetet analyserades 40,697 patienter med förstagångs-hjärtinfarkt, utan tidigare hjärtsvikt och med känd VKEF som överlevt akut hjärtinfarkt. Följsamhet till betablockad studerades under första året efter utskrivning. Det visade sig att 90,7% (n=36,869) erhöll beta-blockad vid utskrivning vilket är högt jämfört med andra motsvarande länder. I följsamhetsanalysen inkluderades patienter som överlevde första året (n=38,597) efter utskrivning och där visade det sig att 31,1% inte har varit följsamma till beta-blockad behandling. Patienter med nedsatt VKEF med eller utan klinisk hjärtsvikt visade högst sannolikhet att vara följsamma, medan patienter med bevarad VKEF med eller utan klinisk hjärtsvikt hade lägre följsamhet. Vid 4 års uppföljning efter infarkten sågs en association med lägre risk för återinläggning på grund av hjärtsvikt, och död hos de infarktpatienter som varit följsamma till behandling.

Hjärtsvikt efter hjärtinfarkt är vanligt med minskande förekomst över tid, troligen som effekt av bättre hjärtinfarktbehandling och förändringar i riskfaktorer. Hjärtsvikt har en fortsatt allvarlig prognos även vid bevarad VKEF. Föreskrivning av betablockad som sekundärprevention är hög oavsett hjärtfunktion och hjärtsvikt men följsamheten är cirka 70%, högst dock hos patienter med hög risk där det förefaller gå betydligt bättre om man är följsam. Sammantaget är det fortsatt viktigt att uppmärksamma nedsatt hjärtfunktion och kliniska tecken på hjärtsvikt vid hjärtinfarkt.

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